

Aprepitant: A substance P antagonist for chemotherapy induced nausea and vomiting

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Abstract

The episodes of nausea and vomiting which follow each cycle of chemotherapy are the most troublesome side effect experienced by cancer patients. Introduction of ondansetron was a definite therapeutic advance in treating chemotherapy induced nausea and vomiting (CINV) with more effectiveness with corticosteroids. However, the protection remained largely limited to acute phase of CINV with little or no effect over delayed phase. Aprepitant, a drug that antagonizes the effect of substance P on neurokinin type 1 receptor showed promising results in controlling both phases of CINV. This drug is well absorbed orally with a t_{max} of about four hours. The addition of aprepitant to ondansetron and dexamethasone was found to be superior to ondansetron and dexamethasone alone in clinical trials with patients taking high and moderate emetogenic chemotherapy. This drug also showed a good safety profile, but its inhibitory effect on CYP3A4 may result in clinically significant drug interactions needing dose modifications of co-administered drugs. The National Comprehensive Cancer Network guidelines for CINV recommends the use of aprepitant with high and moderately emetogenic anticancer drugs. Results of ongoing clinical trials with aprepitant and other agents of this new class of antiemetics are awaited and may alleviate the sufferings of cancer patients.

Key words: Antiemetics, aprepitant, chemotherapy induced nausea and vomiting, neurokinin

Introduction

Nausea and vomiting (emesis) are devastating side-effects of treatment with antineoplastic agents. The patients described nausea and vomiting as the most feared effects of chemotherapy. Chemotherapy induced nausea and vomiting (CINV) are so troublesome to some patients that after repeated cycles of treatment, they will be conditioned to develop these symptoms even before the treatment is given.^[1] Moreover, nausea and vomiting can cause metabolic imbalances, degeneration of self care and functional ability, nutrient depletion, anorexia, decline in patient's performance and mental status, wound dehiscence and esophageal tear.^[2]

During the last few decades, definite progress has been

made in the management of CINV. The introduction of antiemetic drugs including dopamine receptor blockers and serotonin receptor antagonists helped to lessen or prevent nausea and vomiting up to certain extent. Ondansetron is an established treatment for chemotherapy and postoperative nausea and vomiting. The addition of corticosteroids like dexamethasone further improved these symptoms. But unfortunately the effectiveness of these drugs remained largely limited to acute emesis even when started before the first dose of the anticancer drug at each cycle of treatment. The role of currently available drugs in the management of delayed emesis (occurring after 24 h) is very less.^[3] Also none of these drugs or regimens work in all patients, nor do they treat nausea and vomiting once they occur.^[1] So new drugs which take care of both acute

and delayed emesis and which will improve the quality of life in cancer patients undergoing chemotherapy will be of great interest.

Drugs which block substance P from binding to neurokinin type 1 (NK₁) receptors can be of use as antiemetic agents as these neurotransmitters are implicated in the pathoetiology of emesis.^[3] Aprepitant is the first member of this new class of antiemetic drugs which is a potent, selective, CNS-penetrant oral nonpeptide antagonist of NK₁ receptor.^[1] Chemically it is 5-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one).^[4] Studies have shown its effectiveness in both early and delayed emesis induced by chemotherapy.^[5]

Pathophysiology of CINV

The emetic response is primarily a protective reflex that occurs after the ingestion of toxic substances, after certain surgical procedures and as a consequence of a wide variety of diseases. Vomiting is a complex reflex mechanism which involves afferent and efferent pathways and a vomiting center (VC). VC is considered to be situated within the medulla oblongata of the brain stem.^[6] VC has mainly three components, area postrema (AP), nucleus tractus solitarius (NTS) and dorsal motor vagal nucleus (DMVN), which integrates the emetic responses.^[6]

Stimulation of VC can be brought about by a variety of stimuli [Figure 1]. The chemotherapeutic agents or their metabolites present in blood or cerebrospinal fluid

can directly activate the chemoreceptor trigger zone and there by VC.^[7] Anticancer drugs can cause release of serotonin and substance P from the enterochromaffin cells of gastric mucosa, which sends impulses to the VC through the vagal afferent nerve fibers that innervate the gastrointestinal tract (GIT). Disturbances in the vestibular apparatus will also stimulate VC to produce an emetic reflex.^[7] Followed by the stimulation of VC, vomiting is then mediated by various efferent pathways including the vagus and phrenic nerves.^[6]

The stimulation of VC results in the closure of airways and a marked lowering of respiration. This follows the relaxation of the upper portion of the esophagus and increase in intra abdominal pressure leading to expulsion of gastric contents.^[6]

Role of neurotransmitters

Emesis is primarily mediated through neurotransmitters in the central nervous system and the GIT. Among them serotonin, dopamine, substance P, acetylcholine and histamine are well known in this regard.^[8] Therefore, in the treatment of CINV, the antagonists of these neurotransmitter receptors are well-explored and serotonin receptor antagonists remain as the mainstay of treatment with or without corticosteroids.

The importance of substance P and its receptor neurokinin 1 (NK₁) is becoming more evident in the pathophysiology of CINV.^[7] Substance P can induce vomiting after binding to NK₁ receptors in the abdominal vagus, the NTS and the AP. Substance P is one of the many structurally related tachykinin peptides found in the nervous system. The other members of this family are neurokinin A and neurokinin B. Substance P functions as a neurotransmitter in CNS and the vagal afferent neurons in the GIT and also act as a local hormone in enteric nervous system. Substance P is believed to exert a number of central actions that implicate the peptide in nausea, emesis, behavior, anxiety, depression and pain transmission.^[9,10]

The actions of substance P and neurokinin A and B are mediated by three distinct G protein-coupled receptors, NK₁, NK₂ and NK₃.^[6] The majority of central and peripheral effects of substance P are mediated by NK₁ receptors.^[9] NK₁ receptors are dense in NTS and DMVN. NK₁ receptors are also present in the areas of the brain involved in the regulation of affective behaviors and neurochemical response to stress.^[11] The presence of NK₁ receptors on the motor neurons projecting to the greater curvature of stomach indicates that substance P has role in physiological and pathological behavior of the stomach. These actions of

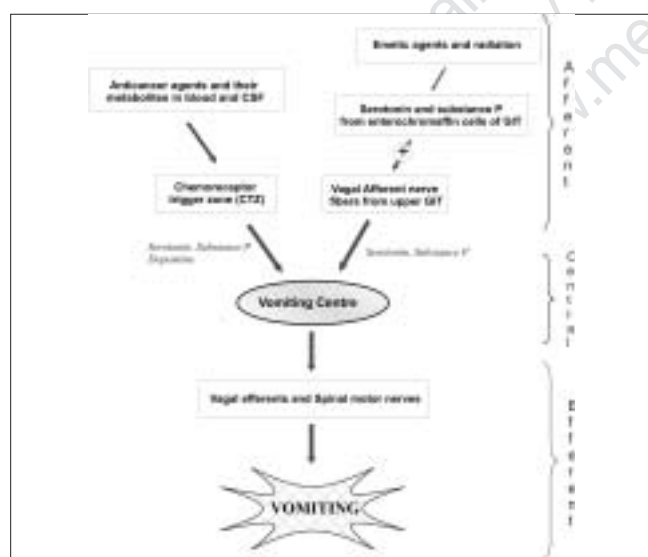


Figure 1: The afferent, central and efferent pathways of chemotherapy induced nausea and vomiting

substance P are mediated *via* the release of nitric oxide and VIP within the enteric nervous system.^[12]

In animal models, the substance P inhibitors exert a more broad antiemetic effect than serotonin inhibitors.^[13] Based on these observations, a new group of drugs that antagonize NK₁ receptors are developed for controlling chemotherapy induced nausea and vomiting. Aprepitant is one such agent, which has shown promising results in CINV in preclinical and clinical studies. Its effectiveness in controlling delayed emesis is particularly noteworthy.^[8]

Pharmacokinetics

Aprepitant exhibit nonlinear pharmacokinetics, indicating saturation of metabolism and decreased clearance with increasing dose.^[14] The oral administration of aprepitant at doses 125 mg on day 1 and 80 mg once daily on days 2 and 3 resulted in AUC_{0-24h} of approximately 19.6 µg hr/ml on day 1 and 21.2 µg hr/ml on day 2. The C_{max} is found to be 1.6 µg/ml on day 1 and 1.4 µg/ml on day 3 with a T_{max} of 4 h. The bioavailability of aprepitant was shown to be 60-65% after an oral dose and food does not interfere with the oral absorption. It is highly bound to plasma proteins (>95%) and the mean apparent volume of distribution at steady state is about 70 L. Aprepitant crosses blood brain barrier in humans and placental barrier in animals.^[15]

Aprepitant undergoes extensive metabolism in liver primarily by CYP3A4 mediated pathways with minor action by CYP1A2 and CYP2C19 enzymes. The apparent plasma clearance of aprepitant ranges from 62-90 ml/min and a t_{1/2} of 9-13 h.^[15]

No clinically significant differences exist in the plasma concentration of aprepitant between males and females after a single 125 mg oral dose. With the three day aprepitant regimen, no dose adjustment is needed in geriatric population even though they are at a higher physiologic risk of dehydration as a result of severe nausea and vomiting.^[15,16]

In patients with mild hepatic insufficiency, aprepitant was well tolerated without the need for any dose reduction. But data are lacking in patients with severe hepatic insufficiency.^[15]

A study by Bergman *et al.*, reported that there were no clinically meaningful differences in the pharmacokinetics of a single 240 mg oral dose of aprepitant between healthy volunteers and patients with end stage renal disease or patients with severe renal insufficiency undergoing hemodialysis. The plasma concentrations of

unbound aprepitant, which is more correlated with pharmacological effects than total aprepitant AUC, is not clinically affected in renal insufficiency patients. Therefore, no dosage adjustment is required in these patients.^[17]

Adverse effects

The results of various clinical trials indicated that the incidence of adverse effects were similar in aprepitant group compared with the group which received only standard regimen. Most commonly observed side-effects with aprepitant treatment were asthenia, hiccups, diarrhea, gastritis, elevation in liver function tests and dizziness. There are also reports of thrombocytopenia and dehydration.^[7,18]

Drug interactions

At therapeutic doses, aprepitant is an inhibitor of CYP 3A4 isoenzyme. So there is risk of drug interactions when co-administered with drugs which are metabolized by CYP3A4. The clinical trials which used aprepitant along with anticancer drugs, namely cyclophosphamide, etoposide, taxanes and vinca alkaloids which use CYP3A4 for metabolism, failed to produce any significant interaction.^[7] The use of aprepitant should be avoided with pimoizidine, terfenadine, cisapride and astemizole due to the potential for life threatening ventricular arrhythmias. A reduction in dose to about 50% is recommended for i.v. dexamethasone and other corticosteroids when given along with aprepitant.^[19]

A clinical trial which assessed the effect of aprepitant on drug metabolizing enzymes recommends a 50% reduction in oral dose of benzodiazepines metabolized by CYP3A4 including midazolam and alprazolam.^[20]

A five-fold increase in AUC and three-fold increase in half-life of aprepitant was noted when given along with ketoconazole, which warrants caution while administering along with azoles.^[15] Other drugs, which need careful monitoring of toxicity are imatinib, irinotecan, nefazodone, nelfinavir, paroxetine and ritonavir.^[15] Aprepitant can produce a transient, modest induction of CYP2C9 activity. This can result in clinically significant interaction with warfarin and phenytoin.^[21]

The anticancer effect of cyclophosphamide and ifosfamide needs activation by CYP3A4. The combination of aprepitant can result in suboptimal plasma concentrations of such chemotherapeutic drugs resulting in decreased anticancer effects.^[7] Patients on oral contraceptives need to use an alternative method of contraception when on therapy.^[22] St. Johns' wort, a widely used herbal drug may decrease aprepitant plasma

concentrations when used concurrently.^[17]

Preclinical and Clinical Trials

There were many attempts made by researchers to find the site and mechanism of action of 5HT₃ receptor antagonists and involvement of other neurotransmitters in the genesis of emetic response.^[23] The induction of emesis by cytotoxic drugs is mediated predominantly through the activation of vagal afferents by serotonin released from enterochromaffin cells in the mucosa of upper gut. The critical role of vagus in emesis induced by cytotoxic drugs was also observed in a range of animal species including ferret, suncus, dog and monkey. This shows the possibility of drugs targeted at other afferent neurotransmitter system (substance P, acetylcholine and CCK-8) as antiemetic agents. It was also noted that 5HT₃ receptor antagonists do not block all components of the emesis induced by cytotoxic drugs or all vagally-mediated emesis. They were also ineffective against centrally acting emetic stimuli induced by motion, loperamide, morphine and apomorphine. This confirmed the involvement of other mediators than 5HT in emetic response.^[23]

A selective NK₁ receptor antagonist, CP-99,994 showed potent, broad spectrum antiemetic activity in dogs and ferrets.^[23] NK₁ receptor antagonists blocked emesis induced by both centrally and peripherally acting agents implicating its central site of action, probably on neurons triggering emesis in dorsal vagal complex. GR 205171, another NK₁ receptor antagonist exhibited high efficacy against both acute and delayed emetic response to cisplatin in piglets.^[24] The protection in delayed emesis was superior in comparison with granisetron. So a broader spectrum of activity with a variety of emetic stimuli and prominent activity in delayed emesis differentiate NK₁ receptor antagonists to 5HT receptor antagonists.

The early clinical trials with aprepitant showed promising results in preventing CINV, notably in delayed emesis than acute emesis compared with 5HT₃ antagonists in patients receiving cisplatin.^[25-27]

In a phase III clinical trial by Hesketh *et al.*,^[18] which included chemotherapy naïve patients receiving cisplatin ≥ 70 mg/m², were given either standard regimen (Ondansetron and dexamethasone on day 1; dexamethasone on day 2-4, n=260) or an aprepitant regimen (aprepitant plus ondansetron and dexamethasone on day 1; aprepitant and dexamethasone on days 2-3 and dexamethasone on day 4). The primary endpoint was complete response on days 1-5 post cisplatin. The patients with complete response were

72.7% in aprepitant group versus 52.3% in standard therapy group, which was statistically significant. The aprepitant group was found superior in separate analysis of both acute phase (89.2% Vs 78.1, $P < 0.001$) and delayed phase (75.4 Vs 55.8%, $P < 0.001$). Aprepitant group was also statistically superior in all comparisons for secondary and exploratory endpoints of no emesis, no rescue therapy and complete protection. The aprepitant regimen was well tolerated with the incidence of adverse events comparable in both groups.

A randomized, double blind, placebo controlled trial conducted in Latin America evaluated the efficacy and tolerability of aprepitant plus standard therapy in 569 cancer patients scheduled to receive treatment with high dose cisplatin. Two hundred and eighty six patients received i.v. ondansetron 32 mg and oral dexamethasone 20 mg on day 1 and oral dexamethasone 8 mg twice daily on days 2-4. The aprepitant group (n=283) received oral aprepitant 125 mg, i.v. dexamethasone 32 mg and oral dexamethasone 12 mg on day 1; oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2-3; and oral dexamethasone 8 mg on day 4. The primary endpoint was complete response (no emesis and rescue therapy) during the 5 day period post cisplatin. During this period the percentage of patients who achieved a complete response were 62.7% in aprepitant group compared to 43.3% in standard therapy group ($P < 0.001$). The complete response rate was significantly high in aprepitant group at day 1 (82.8 Vs 68.4%, $P < 0.001$) and days 2-5 (67.7 Vs 46.8%, $P < 0.001$) with similar adverse events in both groups (72.8 vs. 72.6%).^[28]

A study by de Wit *et al.*^[29] evaluated the sustainability of antiemetic effect of aprepitant in patients receiving multiple cycles of cisplatin-based chemotherapy. The patients were divided into three groups. Group 1 received aprepitant 375 mg 1 h before cisplatin on day 1 and aprepitant 250 mg on days 2-5. Group 2 were given aprepitant 125 mg before cisplatin and aprepitant 80 mg on days 2-5 and group 3 received placebo before cisplatin on day 2-5. All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin and dexamethasone 8 mg on days 2-5. The primary endpoint was complete response over five days following cisplatin in up to six cycles. The results showed the patients with complete response after first cycle was 64% in aprepitant group and 49% in standard treatment group. By the end of sixth cycle the response rate remained almost same (59%) in aprepitant group, but a decline was noted in standard group to 34%. Therefore, they concluded that aprepitant provided better and more sustained protection against CINV over multiple cycles. The superior response with

Table 1: National Comprehensive Cancer Network practice guidelines in oncology for antiemetics-2005^[2]

Risk of emesis	Recommended treatment	Dose of aprepitant	
		Pre-chemotherapy (day 1)	Post-chemotherapy
High (level 5)	Aprepitant + 5HT ₃ antagonist + dexamethasone ± lorazepam	125 mg orally	80 mg/day orally on day 2 and 3
Moderate (level 3 and 4)	Pre-chemo (day 1): 5HT ₃ antagonist + dexamethasone ± lorazepam. Consider aprepitant in selected patients *Post-chemotherapy (day 2-4): 5HT ₃ antagonist or dexamethasone or aprepitant and dexamethasone ± lorazepam	125 mg orally	80 mg/day orally on day 2 and 3

*Aprepitant may be considered in chemotherapy with carboplatin, cyclophosphamide, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate.

aprepitant was also documented in a clinical trial by Herrstedt *et al* in preventing CINV by moderately emetogenic chemotherapy (cyclophosphamide alone or with dexamethasone or epirubicin) over multiple cycles.^[30]

A randomized multi centric clinical trial studied the efficacy of aprepitant for the prevention of CINV in breast cancer patients receiving moderately emetogenic chemotherapy. These treatment naïve patients were taking cyclophosphamide ± doxorubicin or epirubicin. The patients were randomly assigned to either an aprepitant regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8h later; days 2 through 3, aprepitant 80 mg qd) or a control regimen (day 1: ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bd). The primary endpoint was the proportion of patients with complete response, that is no vomiting and no use of rescue therapy. Aprepitant was found to be more effective (50.8% Vs 42.5%, $P=0.015$) with tolerability similar to control group.^[31]

Guidelines on Aprepitant for Treatment of CINV

The risk of emesis in patients receiving chemotherapy of high and moderate emetogenicity last for at least four weeks. The anticancer drugs dacarbazine, streptozocin, mechlorethamine, carmustine (>250 mg/m²), cisplatin (≥ 50 mg/m²) and cyclophosphamide (>1500 mg/m²) have a high emetogenic risk, i.e., greater than 90% of patients experience emesis in the absence of effective antiemetic prophylaxis (level 5). Moderate emetogenic risk is associated with idarubicin, ifosfamide, irinotecan, lomustine etc., (level 3). In moderate emetogenic risk level 4 and 3, 60-90% and 30-60% of patients respectively experience emesis in the absence of effective antiemetic prophylaxis.^[32] Aprepitant

is recommended for high and moderate emetogenic risk chemotherapy.

The National Comprehensive Cancer Network guidelines (NCCN) for chemotherapy induced nausea and vomiting is given in the Table 1. These guidelines are category 1 (uniform NCCN consensus based on high level evidence) for post-cisplatin >50 mg/m² (high emetogenic risk) and post-carboplatin ≥ 300 mg/m², cyclophosphamide ≥ 600 -1000 mg/m², doxorubicin ≥ 50 mg/m² (moderate emetogenic risk). For others it is category 2A (uniform NCCN consensus based on low level evidence).^[2]

Summary

Aprepitant appears to be a promising drug in the treatment of CINV. Its efficacy in controlling the delayed phase of emesis is particularly noteworthy. Moreover, this drug showed a good safety profile in clinical trials. But aprepitant has not been compared to the longer acting serotonin inhibitors, which have also been recommended for delayed nausea and vomiting in moderately emetogenic regimens. Data are also lacking in patients taking multiday chemotherapy, stem cell transplantation and in paediatric patients. Caution is required for potential interactions when co-administered with other drugs. The results from the trials with other NK₁ receptor antagonists like vofopitant, CP-122721, CJ-11794 and L-758298 are also awaited. Cost-benefit of this drug also should be considered before prescribing to the patients.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Announcement

Dr. J. C. Patel Birth Centenary Celebration Committee

The year 2008 is the Birth Centenary Year of Dr. J. C. Patel. Some of his students/admirers felt that it would be a good idea to celebrate this Centenary Year by organizing CMEs, Orations/Lectures, Conferences, etc. during the year. He was associated with many professional bodies, which meet regularly every year; during these annual meetings/conferences, a lecture/symposium, etc can be organized as a part of Centenary celebrations. We would like to form a Dr. J. C. Patel Birth Centenary Celebrations Committee. All his past students/admirers are invited to join the committee (without any financial commitment). Kindly communicate your name, designation, postal address, telephone number and E-mail ID to Dr. B. C. Mehta at Flat 504, Prachi Society, Juhu-Versova Link Road, Andheri (W), Mumbai 400 053 (drmehta.bc@gmail.com).