DRUG REVIEW

Aprepitant- A Novel Drug to Prevent Cancer Chemotherapy Induced Nausea and Vomiting

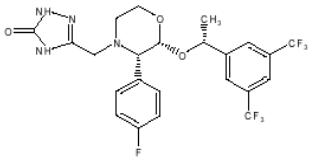
Meenakshi Gupta, Deepika Tikoo

Introduction

Nausea and vomiting are common and distressing side effects of the chemotherapy. However, the drugs used for chemotherapy vary in the extent to which they cause nausea and vomiting. Highly emetogenic drugs like cisplatin result in severe nausea in most patients as compared to moderately emetogenic ones. Agents commonly used for the treatment of chemotherapy induced vomiting include dopamine antagonists, 5HT3 antagonist and corticosteroids (1). Search for the novel agents has led to the development of Aprepitant, which is a neurokinin 1 receptor blocker.

Chemistry and Mechanism of Action

Aprepitant is chemically described as 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.Its empirical formula is C23H21F7N4O3, and its structural formula is:



Aprepitant is a white to off-white crystalline solid (molecular weight: 534.43). It is practically insoluble in water, sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile (2).

Aprepitant is a selective Neurokinin-1 receptor antagonist which is substance P preferring G-protein coupled receptor located in the central nervous system and peripheral nervous system. It has little or no affinity for serotonin, dopamine or corticosteroids receptors. Substance P is a neuropeptide which sends and receives impulses and messages from the brain. It is found in high concentration in the vomiting center of the brain and when activated it results in vomiting reflux. Aprepitant has been shown to inhibit both acute and delayed emesis induced by cytotoxic chemotherapeutic such as cisplatin by blocking substance P. In addition to this, it also plays a key part in transmission of pain impulses from the peripheral receptors to the CNS and is involved in various behavioural, neurochemical and cardiovascular responses to stress (3).

Pharmacokinetics

Aprepitant is given orally and its oral bioavailability is approximately 60 to 65%. The recommended dose of aprepitant is 125 mg orally one hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Following these doses, the Cmax occurs in approximately 4hrs and reaches about 1.5µg/ml. The drug is slowly absorbed, highly bound to plasma protein (95%) and mean volume of distribution is approximately 70L. It crosses the blood brain barrier. The half life of aprepitant is 9-13hrs. Data indicate that aprepitant is extensively metabolized by CYP3A4 and to a lesser degree, by CYP1A2 and CYP2C19. Plasma concentrations of aprepitant may be reduced by CYPP3A4 inducers like carbamazepine, phenytoin and rifampicin and increased by CYP3A4 inhibitors like clarithromycin, ketoconazole, nelfinavir and ritonavir. It is excreted in both urine & faeces (2).

Clinical Use

Addition of aprepitant to standard regimen of ondansetron and dexamethasone provides superior antiemetic protection in patients with cancer, receiving high dose cisplatin based chemotherapy (4). This better antiemetic protection of aprepitant when administered in addition to standard antiemtic therapy (5HT3 antagonist and dexamethasone) is found to be well maintained over multiple cycles of highly emetogenic therapy (5). A recent comparative clinical trial was done to study the effectiveness of a single day three drug regimen of dexamethasone, palonosetron and aprepitant for prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy in breast cancer patients. It showed complete response (no vomiting, no rescue medication) in 76% patients for acute period and 66% for the delayed period (6). The aprepitant

From the Department of Pharmacology, SGRD Institute of Medical Sciences & Research Vallah-Amritsar- India
Correspondence to : Dr. Meenakshi Gupta, Dept of Pharmacology, SGRD Institute of Medical Sciences & Research Vallah-Amritsar

regimen has been shown to reduce the requirement of rescue medication (11%) when compared with the control group (20%) for prevention of chemotherapy induced nausea vomiting (CINV) in Chinese breast cancer patients (7).Aprepitant use in patients receiving high dose chemotherapy with hematopoietic stem cell support resulted in prevention of emesis in majority of patient and was associated with minimal side effects, most common being hiccups (33%) and drowsiness (33%) (8). Aprepitant triple therapy was also found to be well tolerated in adolescent patients and complete response rates were greater than control, although not statistically significant. Pharmacokinetics suggested that adult dosing regimen is appropriate for adolescent patient (9).

Various trials have been carried out to study the other recognized uses of aprepitant apart from its use in CINV. Aprepitant has been successfully used for four months in a patient of refractory diabetic gastroparesis and was found to improve the patient's quality of life and overall glycemic control (10). As substance P is a key mediator in pruritis, it has been suggested that aprepitant causes potential reduction in substance P induced pruritis (11).

It is also used for postoperative nausea and vomiting. The recommended oral dosage is 40 mg within 3 hours prior to induction of anesthesia.Aprepitant has not been studied in pregnant women.

Adverse Effects

Assessing adverse effects in patients who are given multiple drugs for their cancers can be difficult. Adverse events associated with regimens containing aprepitant include weakness, fatigue, feeling listless, constipation, diarrhea, anorexia, hiccups, stomach upset, pain and rarely dizziness and tinnitus (2). A case of ifosfamide induced neurotoxicity after the addition of aprepitant to an antiemetic regimen has been reported (12).

Drug Interactions

Aprepitant reduces plasma concentrations of CYP2C9 substrates like phenytoin and warfarin and increases the plasma levels of CYP3A4 substrates like alprazolam, dexamethasone, etoposide, ifosamide, vinblastine and vincristine (2). Hence, the dose of dexamethasone should be reduced to approximately 50% and the intravenous and oral dose of methylprednisolone to 25% and 50%, respectively, when administering along with aprepitant.

Conclusion

Although the efficacy of aprepitant as an aniemetic in chemotherapy has been proven, questions remain about its role in practice and its effectiveness in subsequent cycles of chemotherapy. Although the results of clinical trial look promising, more studies are warranted.

References

1. Herrstedt J, Aapro MS, Smyth JF. *et al*. Corticosteroids, dopamine antagonists & other drugs. Support Care Cancer 1998 ; 6 : 204-14.
2. Emend capsules (Aprepitant capsules) Drug information: uses, side effects, drug interactions and warnings at RxList. [cited 2009 July 08]. Available from: http://www.rxlist.com/emend-drug.htm.
3. Rupniak NM and Kramer MS. Discovery of the antidepressant and antiemetic efficacy of substance P receptor (NK-1) antagonists. *Trends pharmacol Sci* 1999 ; 20 : 485-90.
4. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD. *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 : 3090-98.
5. deWit R, Herrstedt J, Rapoport B. *et al*. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. *Eur J Cancer* 2004 ; 40 : 403-10.
6. Grunberg SM, Dugan M, Muss H. *et al*. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. *Support Care Cancer* 2009 ; 17 : 589-94.
7. Yeo W, Mo FK, Suen JJ *et al*. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Treat* 2009 ; 113 : 529-35.
8. Paul B, Trovato JA, Thompson J. *et al*. Efficacy of Aprepitant in Patients Receiving High-Dose Chemotherapy with Hematopoietic Stem Cell Support. *J Oncol Pharm Pract* 2009.[Epub ahead of print].
9. Gore L, Chawla S, Petrilli A. *et al*. Aprepitant is adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatr Blood Cancer* 2009 ; 52 : 242-7.
10. Chong K, Dhatariya K. A case of severe, refractory diabetic gastroparesis managed by prolonged use of aprepitant. *Nat Rev Endocrinol* 2009 ; 5 : 285-8.
11. Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Engl J Med* 2009 ; 361 : 1415-6.
12. Jarkowski A 3rd. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. *Am J Health Syst Pharm* 2008 ; 65 : 2229-31.