Review Article

Drug Profile of Aprepitant Regimen for the Prevention of Chemotherapy Induced Nausea and Emesis

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ABSTRACT

The episodes of nausea and vomiting that 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 (APR), a drug that antagonizes the effect of substance P on neurokinin type 1 receptor showed promising results in controlling both phases of CINV. When combined with a standard regimen of corticosteroid (Dexamethasone) and a serotonin 5-HT3 receptor antagonist (Ondansetron), oral Aprepitant (125mg on day 1, 80mg once daily on day 2 and day 3) was effective in the prevention of acute and delayed CINV associated with single or multiple cycles of Highly Emetogenic Chemotherapy (HEC). The addition of Aprepitant to Ondansetron (serotonin 5-HT3 antagonist) and Dexamethasone (corticosteroid) was found to be superior to Ondansetron (OND) and Dexamethasone (DEX) alone in clinical trials with patients taking high and moderate emetogenic chemotherapy. This drug is well absorbed orally with a tmax of about 4 hours. This drug also showed a good safety profile but its inhibitory effect on CYP3A4 may result in clinically significant drug interactions needing dose modification 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 anti-emetics are awaited and may alleviate the sufferings of cancer patients.

Keywords: Aprepitant, Neurokinin 1 receptor, Antiemetics, CINV.

INTRODUCTION

A number of well-conducted trials have formed the basis of today's evidence-based antiemetic guidelines.[1-3] Some aspects of chemotherapy-induced nausea and vomiting (CINV), however, have not been as well studied as others. One such topic is anti-emetic therapy in patients receiving multiple cycles of chemotherapy.[4] Cytotoxic chemotherapy drugs can cause acute nausea and vomiting in the first 24 hours, and then delayed emesis between 2-6 days. Cisplatin is the example of a drug with high emetic potential which means that 90% or more of patients will vomit if they don't receive prophylactic anti-emetics. Anti-emetics are best given prior to the initial course of therapy because patients who vomit after chemotherapy can develop anticipatory emesis prior to subsequent cycles of chemotherapy.[5]

A general impression from various studies is that the antiemetic effect obtained in the first cycle of chemotherapy decreases during subsequent cycles, offering patients poor protection from nausea and emesis during a major part of their chemotherapy.[4]

Two important neuropeptide receptors involved in the mechanism of emesis following chemotherapy treatment have been identified. Serotonin receptors in the GIT and in the CNS are important in the early development of emesis; 5-HT3 receptor antagonists in particular have been shown to provide relief from emesis in experimental animals and patients that have been treated with cytotoxic drugs. [6-7]

Chemotherapy agents stimulate release of serotonin from the GI tract as well as substance P.[8] Substance P also has a role in the emetic reflex; it binds to the NK receptors that are located in the periphery and in the brain stem. Central NK 1 receptors are considered to be most relevant in the emetic pathway.[9,10] In the first 8 hours(acute phase),post chemotherapy emesis is particularly responsive to 5-HT3 receptor antagonist.[11] The delayed phase of CINV is defined as emesis which occurs beyond 24hours of chemotherapy and successful management of this phase rarely exceeded 50%.[12-15] While dexamethasone is considered an important agent in controlling emesis in this delayed phase,[14] much needed improvement of CINV management came with the introduction of the NK 1 receptor antagonist; Aprepitant, a new class of anti-emetics, as well as palonosetron, a long acting 5-HT3 receptor antagonist.[16] Aprepitant crosses the Blood Brain Barrier(BBB) to exert its anti-emetic effect[10] and has been approved for the prevention of CINV in patients receiving HEC and MEC. The antiemetic effect of the APR regimen was maintained and continuously superior to OND plus DEX through six cycles of HEC.[17]Consequently, the three-drug combination including APR is now recommended as antiemetic prophylaxis in this patients.[18]

Dosage and Administration

Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of Aprepitant is 125mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80mg once daily in the morning on Day 2 and 3.

Aprepitant may be taken with or without food.

Mechanism of Action

Aprepitant is a selective high affinity antagonist of human substance P/NK 1 receptors.

NK 1 receptor antagonist prevents both acute and delayed CINV. These agents act centrally at NK1 receptors in vomiting centers within the CNS to block their activation by substance P released as an unwanted consequence of chemotherapy.

Pharmacokinetics

- **Absorption**

  Aprepitant exhibits non-linear pharmacokinetics, indicating saturation of metabolism and decreased clearance with increasing dose. The oral administration of Aprepitant at doses of 125mg on Day 1 and 80mg OD on days 2&3 resulted in AUC_{0-24h} of approximately 19.6 microgram hour/mL on day 1 and 21.2 microgram hour/mL on day 2. The C_{max} is found to be 1.6 mg/mL on day 1 and 1.4 microgram/mL on day 3 with a tmax of 4 hours. The bioavailability of Aprepitant was shown to be 60-65% after an oral dose and food does not interfere with its oral absorption.[19]

- **Distribution**

  It is highly bound to plasma proteins and mean apparent VD at steady state is about 70L.[20]

- **Metabolism**

  Aprepitant undergoes extensive metabolism. It is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9 or CYP2E1 was detected. Seven metabolites of Aprepitant, which are only weakly active, have been identified in human plasma.[20]

- **Excretion**

  Aprepitant is eliminated primarily by metabolism; it is not renally excreted.

  The apparent plasma clearance of Aprepitant ranged from approximately 62-90mL/min.

  The apparent terminal half-life ranged from approximately 9-13 hours.

Pharmacodynamics

Aprepitant, an anti-emetic, is a substance P or NK1 receptor antagonist which, in combination with other anti-emetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of HEC.

Aprepitant is a selective high affinity antagonist of human substance P or NK1 receptors. Aprepitant has little or no affinity for 5HT3 dopamine and corticosteroid receptors, the targets of existing therapies for CINV.

Drug Interactions

Aprepitant is a substrate, a moderate inhibitor and an inducer of CYP3A4. It is also an inducer of CYP2C9, 5HT3 antagonist: in clinical drug interaction studies, Aprepitant did not have clinically important effects on the pharmacokinetics of Ondansetron, Granisetron or Hydrodolasetron.

Table below shows the drug-drug interactions with Aprepitant.

Table 1

Sl.no	Interacting drugs	Recommended adjustments
1.	Dexamethasone [21,22]	Requires up to 50% dose reduction.
2.	Methyl prednisolone[21,23,24]	• Oral: requires 50% dose reduction • IV : requires 25% dose reduction
3.	Docetaxel[25]	Dose adjustment not required.
4.	Warfarin [26]	Requires 2 weeks of INR monitoring.
5.	Ethinyl estradiol, Norethindrone	Requires secondary barrier contraception.
6.	Ketoconazole	Dose adjustment required.

Adverse Drug Reactions

- COMMON
  - Fatigue
  - Dehydration
  - Abdominal pain
  - Dizziness
  - Constipation
  - Diarrhea

- Epigastric discomfort
- Gastritis
- Anorexia
- Headache
- Alopecia

➢ SERIOUS

- Enterocolitis
- Febrile neutropenia
- Neutropenic sepsis
- Pneumonia
- Sinus tachycardia
- Acne diaphoresis
- Rashes

➢ Laboratory adverse reports were

- Increased AST/ALT- generally mild and transient.[27]

Use in Special Population

➢ Gender, hepatic and renal insufficiency - No dosage adjustment required.
➢ Pregnancy - No adequate and well controlled studies.
➢ Nursing mother - Due to the potential tumorigenecity, it is advised to discontinue therapy.
➢ Pediatric use - Safety and efficacy have not been established.
➢ Geriatric use - Dosage adjustment not required.[27]

Contraindications

Aprepitant is a moderate CYP3A4 inhibitor, it should not be used concurrently with pimozide, terfinadine, astemizole, cisapride. Inhibition of CYP3A4 by Aprepitant could result in elevated plasma concentration of these drugs, potentially causing serious or life threatening reactions.[27]

CONCLUSION

The addition of Aprepitant to standard therapy has improved emesis in both acute and delayed phases of CINV, thereby addressing this unmet need in CINV patients as chemotherapy compliance and quality of life are enhanced with its use.

Accordingly, major anti-emesis guidelines such as European Society for Medical Oncology, the Multinational Association for Supportive Care in Cancer and the American Society of Clinical Oncology, now recommend Aprepitant as part of standard anti-emetic therapy in high risk patients.[28-30]

Most Drug-Drug Interactions with Aprepitant have little or no clinical consequences. It is important that these Drug interactions be put into perspective to help clarify the usefulness of and need for Aprepitant in patients at high or moderate risk from CINV.

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