Aprepitant for Chemotherapy-Induced Nausea and Vomiting

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Although the development of serotonin receptor antagonists has greatly improved treatment for chemotherapy-induced nausea and vomiting, patients receiving chemotherapy continue to experience this troublesome side effect. On March 26, 2003, the U.S. Food and Drug Administration approved aprepitant (Emend®, Merck & Co., Inc., Whitehouse Station, NJ) for use in combination with standard antiemetic agents for acute and delayed nausea and vomiting with initial and repeat courses of highly emetogenic therapy. Aprepitant appears to provide superior control of acute and delayed emesis compared to standard antiemetic therapy. Aprepitant was well tolerated in phase III studies, with side effects similar to standard therapy. Healthcare providers need to be aware of potential drug interactions with aprepitant. Oncology nurses continue to play a key role in helping patients adhere to their antiemetic schedules, stressing the importance of prevention of nausea and vomiting.

Key Words: nausea, vomiting, antiemetics

Researchers have found that patients receiving cisplatin have better control of delayed emesis if they have complete control of acute emesis. Additionally, patients who have experienced delayed nausea and emesis are more likely to develop anticipatory symptoms and have increased difficulty with nausea and vomiting in subsequent chemotherapy cycles (de Wit et al., 1998, 2002; Morrow & Roscoe, 1997).

Standard therapy for acute nausea and vomiting associated with highly emetogenic chemotherapy is a combination of corticosteroids with a serotonin receptor antagonist (Gralla et al., 1999; National Comprehensive Cancer Network, 1997). A corticosteroid plus either a serotonin receptor antagonist or metoclopramide is used commonly for delayed chemotherapy-induced nausea and vomiting (Gralla et al.; Italian Group for Antiemetic Research, 1997). Acute nausea and, particularly, delayed nausea continue to be a major concern for patients with cancer (Griffin et al., 1996). In a recent study of patients receiving serotonin receptor antagonists, the frequency of occurrence of delayed nausea was almost twice that of acute nausea (Hickok et al., 2003).

Clinical Trials of Aprepitant

Substance P was discovered in 1931 and is the most abundant neurokinin in the central and peripheral nervous system (Wahlestedt, 1998). Animal studies have shown that administration of an NK-1 receptor antagonist was effective protection against acute and delayed cisplatin-induced emesis (Rudd, Jordan, & Naylor, 1996; Tattersall et al., 1996).

A phase II clinical trial found that dexamethasone given in combination with an NK-1 receptor antagonist was statistically
superior (p < 0.05) in the prevention of delayed nausea and vomiting compared to dexamethasone given in combination with a serotonin receptor antagonist (Van Belle et al., 2002). In other clinical trials, NK-1 receptor antagonists prevented delayed emesis and improved prevention of acute emesis when given in combination with a serotonin receptor antagonist and corticosteroids (Campos et al., 2001; Navari et al., 1999).

A large, phase III, randomized, double-blind trial (N = 523) was conducted to evaluate the efficacy and tolerability of aprepitant with standard antiemetic therapy in patients receiving high-dose cisplatin (> 70 mg/m²). One group received standard therapy, consisting of IV ondansetron 32 mg and oral dexamethasone 20 mg on day 1 and oral dexamethasone 8 mg twice daily on days 2–4. Another group received oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2–3 and oral dexamethasone 8 mg on day 4. Complete response (no emesis and no rescue therapy) was reported in 62.7% of the aprepitant group and 43.3% of the standard therapy group. For day 1, the acute emesis phase, the complete responses for the aprepitant group and standard therapy group were 82.8% and 68.4%, respectively. For days 2–5, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group. The adverse reactions were similar between the two groups. The aprepitant regimen was well tolerated and demonstrated superior control of acute and delayed emesis compared to standard therapy (Poli-Bigelli et al., 2003). The standard therapy group did not receive the manufacturer’s recommended dose of ondansetron on days 2 and 3.

As patients receive subsequent cycles of chemotherapy, the effectiveness of standard antiemetic therapy decreases. However, the combination of standard antiemetic therapy and aprepitant has demonstrated a constant level of protection against chemotherapy-induced nausea and vomiting in subsequent cycles of chemotherapy. This shows an increase of 10%–15% protection in the acute vomiting phase and 20%–30% protection in the delayed vomiting phase compared to standard antiemetic therapy. Therefore, protection against delayed emesis compared to standard therapy has almost doubled (de Wit, 2005).

Aprepitant Dosage and Administration

Aprepitant is given for three days as part of a regimen that includes corticosteroids and a serotonin receptor antagonist. The recommended dose of aprepitant is 125 mg orally one hour prior to chemotherapy administration (day 1), and 80 mg once daily in the morning on days 2 and 3 (Chawla et al., 2003; Merck & Co., Inc., 2003). Aprepitant has not been studied for the treatment of established nausea and vomiting and, because it is an oral agent, may be of limited benefit to patients who are vomiting. Chronic continuous administration has not been studied and currently is not recommended. Aprepitant may be taken with or without food. No dosage adjustment is necessary for the elderly, patients with renal insufficiency, those with end-stage renal disease undergoing hemodialysis, or patients with mild to moderate hepatic insufficiency (Child-Pugh score = 5–9). No clinical data exist in patients with severe hepatic insufficiency (Child-Pugh score > 9) (Merck & Co., Inc.).

Aprepitant is supplied in a unit-of-use trifollic pack containing one 125 mg capsule and two 80 mg capsules. Aprepitant also is supplied as unpackaged pills. The 125 mg capsule is an opaque, hard gelatin capsule with a white body and pink cap with “462” and “125 mg” printed radially in black ink on the body. The 80 mg capsule is a white, opaque, hard gelatin capsule with “461” and “80 mg” printed radially in black ink on the body. Aprepitant should be stored at 20°–25°C (Merck & Co., Inc., 2003).

Drug Interactions

Aprepitant is a substrate and acts as a moderate inhibitor of CYP3A4 initially and later as an inducer of CYP3A4. Therefore, aprepitant has multiple drug interactions that can lead to increased or decreased plasma concentrations of aprepi tant as well as concomitant drugs (Merck & Co., Inc., 2003). Aprepitant can significantly increase the plasma concentrations of and is contraindicated with pimozide, terendane, astemizole, and cisapride. Aprepitant increases plasma concentrations of certain chemotherapy agents metabolized by CYP3A4, including docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials, aprepi tant was given with docetaxel, vinblastine, vincristine, and ifosfamide without dose adjustments for possible interactions. However, because of the small sample size, particular caution and careful monitoring are advised (Merck & Co., Inc., 2003).

Aprepitant lowers the plasma concentrations of warfarin, tolbutamide, phenytoin, and other drugs known to be metabolized by CYP2C9. Patients on chronic warfarin therapy should have international normalized ratio levels closely monitored for a two-week period, especially 7–10 days after aprepi tant administration. Aprepitant also can decrease the effectiveness of oral contraceptives, so an alternative form of birth control should be used (Merck & Co., Inc., 2003).

The pharmacokinetic effects of aprepi tant are different when coadministered with oral CYP3A4 substrates as opposed to IV CYP3A4 substrates. The oral dose of dexamethasone concurrently administered with aprepi tant should be 50% of the dose that would be given without it. Phase III studies used dexamethasone 12 mg orally on day 1 and dexamethasone 8 mg orally on days 2–4 when given with aprepi tant. Standard therapy without aprepi tant is dexamethasone 20 mg on day 1 and dexamethasone 8 mg twice a day on days 2–4. IV methylprednisolone should be reduced by 25% and oral methylprednisolone reduced by 50% to achieve plasma levels similar to when they are given without aprepi tant (McCrea et al., 2003).

Tolbutamide given with aprepi tant results in decreased plasma concentration of tolbuta midine. Midazolam or other benzodia zepines administered with aprepi tant increase plasma concentrations of these agents. Ketoconazole coadministered with aprepi tant causes increased plasma concentrations of aprepi tant. Rifampin coadministered with aprepi tant decreases plasma concentrations of aprepi tant, reducing its efficacy. Diltilazem coadministered with aprepi tant causes increased plasma levels of both agents. Paroxetine given with aprepi tant results in decreased plasma concentrations of both agents. Therefore, all of these agents should be administered with caution when given in combination with aprepi tant (Merck & Co., Inc., 2003). Current ongoing studies will address many of these drug interactions.

Contraindications and Adverse Effects

Aprepitant generally has been well tolerated. In clinical trials of aprepi tant, adverse events reported in 10% or more of patients included asthenia and fatigue, constipation, diarrhea, nausea, anorexia, and hiccups (Chawla et al., 2003; Merck & Co., Inc., 2003; Poli-Bigelli et al., 2003). Laboratory adverse events reported in 3% or more of patients included increased alanine amino transferase levels, mild and transient increased aspartate amino transferase levels, increased blood urea nitrogen, increased serum creatinine, and proteinuria. In clinical trials of aprepi tant, serious adverse events reported regardless of causality included bradycardia, disorientation, and perforating
duodenal ulcer. In addition, one patient receiving aprepitant developed Stevens-Johnson syndrome; however, the patient also was receiving other medications that have been associated with the condition. Aprepitant is contraindicated in patients who are hypersensitive to any component of the product (Merck & Co., Inc.; Poli-Bigelli et al.).

Implications for Nursing Practice

Oncology nurses continually offer guidance regarding symptom management during chemotherapy. Nausea and vomiting impacts quality of life when it interferes with daily activities. Psychosocial symptoms, which are of great concern to patients with cancer, include concern for family members and partners, effects on work and home duties, anxiety, and depression. As more cancer treatments are administered on an outpatient basis, increased demand is placed on patients’ families (Griffin et al., 1996). Patients and families have become primarily responsible for the identification and management of side effects in the home.

Therefore, nurses must have knowledge about the mechanisms of action of different antiemetics, the emetogenic potential of chemotherapy agents, and independent patient variables that influence nausea and vomiting. Patient variables that increase risk of chemotherapy-induced nausea and vomiting include female gender and age younger than 35. Other potential risk factors include a history of hyperemesis with pregnancy and susceptibility to motion sickness. Interestingly, patients with a history of chronic alcohol intake have reported better control of nausea and vomiting than nondrinkers (Wickham, 2003).

Oncology nurses must emphasize the biphasic nature of cisplatin during patient and family teaching and the importance of taking antiemetics as ordered. Patients who do not have adequate control in the acute phase tend to experience delayed emesis as well. Delayed emesis occurring with repeated cycles of cisplatin can lead to anticipatory nausea and vomiting. This is a form of classical conditioning and is extremely hard to control and very upsetting to patients with cancer (Ossi, Anderson, & Freeman, 1996). Nurses play a key role in helping patients adhere to their antiemetic schedules, stressing the importance of prevention of nausea and vomiting.

A thorough patient medication history should be performed to identify drugs that have the potential to interact with aprepitant. Oncology nurses also need to assess antiemetic effectiveness with every chemotherapy cycle. In a study, healthcare providers’ perceptions of chemotherapy-induced nausea and vomiting were different from actual patient reports of nausea and vomiting. In the study, physicians and nurses perceived patients experiencing complete protection against acute nausea and vomiting to be at least 11% higher than actual patient diary reports. Similarly, patients reported complete protection against delayed nausea and vomiting to be at least 32% lower than healthcare professionals perceived (Grunberg, Hansen, Deuson, & Mavros, 2002). Therefore, chemotherapy-induced nausea and vomiting appears to be understated and undertreated by healthcare professionals and remains an area for improvement. Aprepitant represents a novel agent to improve acute and delayed chemotherapy-induced nausea and vomiting in patients with cancer receiving highly emetogenic therapy such as cisplatin.

Although safety and clinical efficacy are the most important issues in choosing an antiemetic regimen, cost is very much an issue for patients. The cost of aprepitant is overwhelming at $2976.63 for a cycle of chemotherapy ("Aprepitant [Emend] for prevention of nausea and vomiting due to cancer therapy,” 2003). However, Merck & Co., Inc., has reimbursment specialists who investigate insurance coverage for patients. Merck also offers patient assistance to qualified individuals. The phone number for patients or healthcare professionals is 1-866-EMEND Rx. Oncology nurses should be cost-conscious and work in conjunction with physicians and pharmacists to determine the most efficacious, convenient, and cost-effective regimens.

Conclusion

Aprepitant represents a new class of antiemetics that has been proven effective for both acute and delayed chemotherapy-induced nausea and vomiting. Aprepitant was well tolerated in phase III studies, with side effects similar to standard antiemetic therapy. Aprepitant appears to provide superior control of acute and delayed emesis compared to standard therapy. Healthcare providers should be aware of potential drug interactions with aprepitant. Further studies are needed to determine the efficacy of prolonged aprepitant dosage schedules in conjunction with multiple-day chemotherapy regimens. Additionally, palonosetron (Aloxi™, MGI Pharma, Inc., Bloomington, MN), a next-generation serotonin receptor antagonist, recently was approved for acute and delayed chemotherapy-induced nausea and vomiting. Future studies of concomitant administration of palonosetron and aprepitant will be of interest.

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Aprepitant for Chemotherapy-Induced Nausea and Vomiting

- Aprepitant is indicated for use in combination with standard antiemetic therapy for acute and delayed chemotherapy-induced nausea and vomiting.
- The recommended dose of aprepitant is 125 mg orally one hour prior to chemotherapy treatment on day 1 and 80 mg once daily in the morning on days 2 and 3.
- A thorough medication history must be completed to identify potential drug interactions.
- The safety profile of aprepitant is comparable to standard antiemetic therapy.
- Oncology nurses must educate patients regarding their antiemetic schedules, stressing the importance of prevention of chemotherapy-induced nausea and vomiting.