

Continuing Education for Pharmacists

Volume XXI, No. 12

New Drugs of 2003 for Treatment of Nausea and Vomiting from Cancer Chemotherapy: Aloxi and Emend

Thomas A. Gossel, R.Ph., Ph.D.
Professor Emeritus
Ohio Northern University
Ada, Ohio

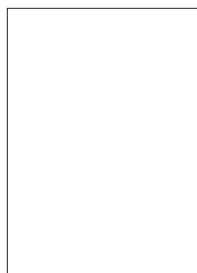
and

J. Richard Wuest, R.Ph., Pharm.D.
Professor Emeritus
University of Cincinnati
Cincinnati, Ohio

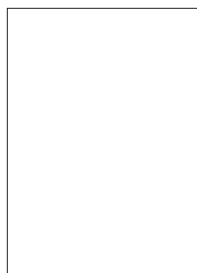
Goals. The goals of this lesson are to provide background information on nausea and vomiting associated with cancer chemotherapy, and review new drugs approved in 2003 for their treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. discuss the etiology and incidence of nausea and vomiting associated with cancer chemotherapy, and identify the risk factors associated with their onset;
2. exhibit knowledge of the pharmacologic classification and



Gossel



Wuest

therapeutic considerations for the drugs discussed; and

3. select from a list, the indications, mechanisms of action, adverse effects and toxicities, drug interactions, and benefits and limitations of the drugs presented.

Two new drugs were approved during 2003 to treat nausea and vomiting (emesis) associated with cancer chemotherapy. Information about the new drugs is summarized in Table 1.

Overview

Paramount in the treatment of cancer is prevention and control of

nausea and vomiting caused by cancer chemotherapeutic drugs and associated treatment. Nausea and the act of vomiting that accompanies it are usually thought of as protective reflexes that help the body rid itself of toxic substances that have entered the stomach or upper portion of the small intestine. Nausea and vomiting also are upsetting to cancer patients and their families. Loss of appetite with nutritional depletion and esophageal rupture, fractures, and wound tearing can result. Intense gastrointestinal (GI) distress can lead to serious metabolic abnormalities, deterioration of the patient's physical and mental status leading to lethargy and depression, premature withdrawal from cancer chemotherapy protocols, and degeneration of functional ability. Quality of life can be affected so adversely that patients may refuse chemotherapy treatment.

Nausea is a subjective phenomenon of an unpleasant sensation experienced in the back of the throat

Table 1
New Drugs for Treatment of Nausea and Vomiting Associated with Cancer Chemotherapy

Trade/Generic Name (Sponsor/Manufacturer)	Dosage Form	Indication	Date Approved
Emend/aprepitant (Merck Human Health)	80 & 125mg capsule	Prevention of acute & delayed nausea & vomiting associated with highly emetogenic cancer chemotherapy	3/03
Aloxi/palonosetron (Helsinn Healthcare SA)	0.25mg/5mL injection	Prevention of acute & delayed nausea & vomiting associated with moderately and highly emetogenic cancer chemotherapy	7/03

This lesson is provided by an educational grant from

PHARMACIA

Table 2
Classification System for Nausea and Vomiting

Anticipatory nausea and vomiting

- Nausea and/or vomiting that occur before the beginning of a new cycle of chemotherapy
- Events that occur in response to conditioned stimuli such as the odors, sights, and sounds of the treatment room
- A classically-conditioned response that typically occurs after three or four prior chemotherapy treatments in which the patient experienced acute or delayed nausea and vomiting

Acute nausea and vomiting

- Nausea and vomiting experienced during the first 24-hour period after chemotherapy administration

Delayed (or late) nausea and vomiting

- Nausea and vomiting that occur more than 24 hours after chemotherapy administration

Chronic nausea and vomiting in advanced cancer patients

- Nausea and vomiting associated with a variety of potential etiologies
- A definitive understanding of the cause is not well known, nor well researched
- Potential causal factors include gastrointestinal, cranial, metabolic, and non-chemotherapeutic drug-induced (e.g., morphine)

and/or upper GI tract that may or may not lead to vomiting. Vomiting is the forceful removal of contents of the stomach, duodenum, or jejunum through the mouth. Retching, also referred to as “dry heaves,” is the presence of gastric and esophageal movements (spasms) associated with vomiting without expulsion of vomitus.

Classification. Nausea and vomiting have been classified by various means including acute, delayed (or late), persistent, chronic, anticipatory, breakthrough, or refractory. The events have also been categorized by response to type

of treatment (e.g., chemotherapy-induced or radiation-induced), and clinical course (e.g., advanced or terminal disease). The most commonly described types, useful to discussion in this lesson, are acute, delayed, and anticipatory chemotherapy-induced nausea and vomiting. Chronic nausea and vomiting associated with advanced cancer is a separate type related to the disease process itself (or non-chemotherapy treatments) that occur in approximately 20 to 70 percent of these patients. It is not discussed in this lesson. Table 2 summarizes major differences between the various types of nausea and vomiting.

Etiology. Both nausea and vomiting are mediated by the CNS, but by separate mechanisms. Nausea is controlled through the autonomic nervous system. Vomiting is caused by stimulation of a complex reflex that is coordinated by the vomiting center located in the lateral reticular formation of the mid-brainstem adjacent to the chemoreceptor trigger zone (CTZ). The vomiting center receives afferent (i.e., incoming) stimulation from several neurologic pathways, including the following:

- the chemoreceptor trigger zone;
- the cerebral cortex and the limbic system in response to sensory stimulation (particularly smell and taste), psychological distress, and pain;
- the vestibular-labyrinthine apparatus of the inner ear, in response to body motion;
- peripheral stimuli from visceral organs and vasculature (via vagal and spinal sympathetic nerves) as a result of exogenous chemicals and endogenous substances that accumulate during inflammation, ischemia, and irritation.

The CTZ is located in the area postrema portion of the brain. This is a highly vascularized site with blood vessels that lack tight junctions between capillary endothelial cells. The CTZ thus lacks a blood-

brain barrier. Chemical substances present in the circulating blood and cerebrospinal fluid (CSF) can, therefore, readily diffuse into the CTZ. Acute emesis following exposure to chemotherapy and other irritant drugs and chemicals is stimulated by release of neurotransmitters in response to the presence of toxic substances in the blood or CSF. Cells within the CTZ, and enterochromaffin cells within the intestinal mucosa, initiate the stimuli that ultimately converge on the vomiting center to stimulate it into action. Enterochromaffin cells comprise a group of basilar granular cells located in the GI tract that synthesize and store serotonin and possibly other neurotransmitters, including substance P and enkephalins.

Each of the above-mentioned pathways contributes to nausea and vomiting in a complex fashion. The fact that so many systems are involved, the variable factors (i.e., dosage, administration route, exposure duration), and emetogenic profile (i.e., time to onset, symptom severity, and duration) account for the increased potential for causing nausea and vomiting.

Risk Factors. Nausea and vomiting do not occur in all cancer patients. The most common causes are irritating chemotherapy drugs and radiation therapy directed to the GI tract, liver, or brain. In addition, several patient characteristics have also been identified. These include the patient’s age and gender, incidence and intensity of nausea and vomiting associated with previous courses of chemotherapy, and history of chronic alcohol use. Patients who experienced severe nausea and vomiting during previous chemotherapy treatments are more likely to experience them in subsequent cycles. Nausea and vomiting are more likely to occur in women and patients <50 years of age. Interestingly, the events are less likely to occur in patients with a history of chronic, high alcohol intake.

Other factors include fluid and electrolyte imbalances such as hypercalcemia, volume depletion, or water intoxication; constipation; opioid use; tumor growth in the GI tract, liver, or central nervous system; infection or septicemia; and uremia. The patient's psychological state, including degree of anxiety during chemotherapy infusions and pretreatment expectations for nausea and vomiting (i.e., self-fulfilling prophecy), is another significant predictor of post-treatment nausea and vomiting.

Anticipatory Nausea and Vomiting. Anticipatory nausea occurs in approximately 30 percent of patients receiving chemotherapy, and anticipatory vomiting in about 11 percent of patients. It was believed that with introduction of the serotonin (5-HT₃) antagonists (e.g., ondansetron/Zofran, dolasetron/Anzemet), the prevalence of anticipatory nausea and vomiting could be greatly reduced. Studies to-date continue to show mixed results, however.

Numerous variables have been investigated as causative factors in anticipatory nausea and vomiting. Although there is little formal agreement on which factors correlate positively with the conditions, a patient with three or more of the following eight characteristics is likely to develop anticipatory nausea and vomiting.

- Age <50 years
- Nausea/vomiting after the last chemotherapy session
- Post-treatment nausea described as "moderate, severe, or intolerable"
- Post-treatment vomiting described as "moderate, severe, or intolerable"
- Sensation of warmth over the body following the last chemotherapy session
- Sweating after the last chemotherapy session
- Generalized weakness following the last chemotherapy session
- Susceptibility to motion sickness

Other variables which have also been correlated with anticipatory nausea and vomiting are listed below.

- High anxiety in response to specific situations
- Highly reactive autonomic nervous system with slow reaction time
- Patient expectation of chemotherapy-related nausea before beginning treatment
- Percentage of previous infusions of chemotherapy followed by nausea
- Post-chemotherapy dizziness
- Lightheadedness
- Long latency of onset of post-treatment nausea and vomiting
- Emetogenic potential of chemotherapeutic agents (i.e., drugs with a moderate to severe potential for post-treatment nausea and vomiting are more likely to cause anticipatory nausea and vomiting)

Treatment of Anticipatory Nausea and Vomiting. Antiemetic drugs do not control anticipatory nausea and vomiting once it has developed. A number of behavioral steps including hypnosis, biofeedback, progressive muscle relaxation, and distractions such as music and video games have been suggested as means of control. Patient referral to a psychologist or other mental health professional who has specific experience in working with cancer patients is recommended when anticipatory nausea and vomiting is identified and deemed to be a significant problem. The earlier it is identified, the greater is the likelihood that treatment will be effective.

Acute Emesis. The incidence and intensity of acute emesis in cancer patients who receive chemotherapy varies according to numerous influencing factors, including the particular drug, dose, schedule and route of administration, and individual variables specific to the patient. These symptoms can be prevented or controlled in the vast majority of cancer patients. Specific

risk factors for acute emesis include:

- inadequate control with previous chemotherapy;
- female gender;
- young age.

The dosage and administration schedule are also extremely important factors. To illustrate, a drug classed as having a low emetogenic potential that is given in high doses may have a great potential to induce nausea and vomiting. The use of drug combinations must also be considered. Most patients receive combination chemotherapy. Therefore, the emetogenic potential of all of the drugs when taken together, as well as individual drug doses, must be considered.

Delayed Emesis. Delayed (or late) nausea and vomiting are responses that occur more than 24 hours after chemotherapy administration. Patients who experience acute emesis following chemotherapy are more likely to have delayed emesis. All predictive characteristics for acute emesis listed above are risk factors for delayed emesis.

Treatment of Acute/Delayed Emesis. The strategy for controlling acute/delayed nausea and vomiting is based on intervention of neurochemical pathways. The precise mechanism is not well defined, but peripheral neuroreceptors and the CTZ contain receptors for serotonin, histamine (H₁ and H₂), dopamine, acetylcholine, substance P, opioids, corticoids, and numerous other endogenous neurotransmitters. Many antiemetics, including the two newly approved drugs, act by competitively blocking receptors for selective neurostimulatory substances, thereby blocking activation of peripheral nerves at the CTZ, and perhaps at the vomiting center.

Palonosetron (Aloxi)

Palonosetron binds strongly and selectively with 5-HT₃ receptors to block serotonin. There is strong

evidence that cancer chemotherapeutic drugs aggravate nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, which then stimulates 5-HT₃ receptors on vagal afferents to initiate the vomiting reflex.

Adverse Effects. In clinical trials that investigated prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, adverse reactions were similar in frequency and severity to those reported for ondansetron or dolasetron. Adverse events noted by ≥ 2 percent of patients in these studies included headache, constipation, diarrhea, dizziness, fatigue, abdominal pain, and insomnia. The drug has been safely administered to patients with pre-existing cardiac impairment. Still, it must be administered with caution in persons prone to develop prolonged cardiac conduction intervals, especially QTc. This includes individuals with congenital QT syndrome, those with hypokalemia or hypomagnesemia, and persons taking potent diuretics, antiarrhythmics, or other drugs that cause QT prolongation.

Drug Interactions. The potential for clinically significant drug interactions with palonosetron is low since the drug is eliminated from the body through both renal excretion and metabolic pathways. Palonosetron does not appear to inhibit or induce cytochrome P450 enzymes.

Indications and Uses. Aloxi is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Dosage and Administration. Aloxi is available in vials containing 0.25mg palonosetron per 5mL. The recommended dosage in adults is 0.25mg infused intravenously over 30 seconds, administered as a single

dose approximately 30 minutes before the onset of chemotherapy. Repeated dosing within a seven-day interval is not recommended because the safety and efficacy of frequent dosing in patients has not been evaluated. Aloxi should not be mixed with other drugs in the same infusion line or I.V. tubing.

Aprepitant (Emend)

Aprepitant is a selective antagonist of human substance P/neurokinin 1 (NK₁) receptors. Antagonists of the subtype NK₁ receptors have been shown to have potent antiemetic activity. Aprepitant is the first entry in this new pharmacologic class of drugs. It has high affinity for NK₁ receptors, but little or no affinity for 5-HT₃, dopamine, and cortisol receptors, popular targets of current treatment for chemotherapy-induced nausea and vomiting.

Aprepitant inhibits emesis induced by chemotherapeutic agents via central actions. It readily crosses the blood brain barrier and binds with brain NK₁ receptors. Studies in animals and humans show that Emend potentiates the antiemetic activity of the 5-HT₃ antagonist ondansetron and the corticosteroid dexamethasone. It inhibits both the acute and delayed phases of cisplatin-induced emesis.

Adverse Effects. Clinical adverse events were experienced in approximately 69 percent of patients treated with aprepitant, compared with approximately 68 percent of patients treated with standard antiemetic therapy. Adverse experiences reported at an incidence of ≥ 3 percent during Phase III studies include effects on the body as a whole (asthenia, fatigue, dehydration, dizziness); gastrointestinal/nutritional (anorexia, abdominal pain, diarrhea, epigastric discomfort, gastritis, heartburn, nausea, vomiting); CNS (headache, insomnia); and tinnitus, neutropenia, and hiccups.

Drug Interactions. Aprepitant undergoes extensive metabolism by

CYP3A4 with less metabolism by CYP1A2 and CYP2C19; it is not excreted renally. Since aprepitant is a moderate inhibitor of the CYP3A4 pathway, it should not be given concurrently with pimozide. Its manufacturer, Merck Human Health, lists coadministration as a contraindication. Inhibition of CYP3A4 could result in elevated plasma concentrations to cause potentially serious toxicity.

Indications and Uses.

Emend, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Dosage and Administration.

Emend is supplied as capsules containing 80 or 125mg aprepitant. It is administered for three days as part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist. The recommended dose is 125mg orally one hour prior to chemotherapy treatment (Day 1) and 80mg daily in the morning on Days 2 and 3. Emend has not been studied for the treatment of established nausea and vomiting.