



Management of Chemotherapy-Induced Nausea and Vomiting

Clinical Significance

Chemotherapy-induced nausea and vomiting continues to have a great impact on the quality of life of patients receiving some anti-neoplastic therapies (Cohen, de Moor, Eisenberg, Ming, and Hu, 2007). CINV can be defined as acute CINV, delayed CINV or anticipatory CINV. Acute CINV occurs within 24 hours after chemotherapy infusion. Delayed CINV begins 24 hours or more after chemotherapy infusion and can last up to several days after chemotherapy infusion is completed. Anticipatory CINV can occur in up to 25% of patients and is a result of classic operant conditioning from stimuli associated with chemotherapy; usually occurring within 12 hours prior to treatment administration (Camp-Sorrell, 2005). In addition to acute, delayed and anticipatory CINV, patients can also experience breakthrough or refractory CINV, which occurs despite prophylactic antiemetic administrations.

According to Cohen, de Moor, Eisenberg, Ming and Hu (2007) 38% of patients receiving a new chemotherapy regimen develop acute CINV and as many as 64% develop delayed CINV. Cohen et al. (2007) also showed that the risk of developing CINV was highly related to having CINV in the previous cycle, illustrating the importance of proper management of CINV at initial treatment. Ballatori (2007) found that more than 90% of patients who experience acute or delayed CINV also reported an impact on their daily activities. Shih, Xu, and Elting (2007) revealed the direct medical cost of working age adults with uncontrolled nausea and vomiting is \$1300.00 per month above their counterparts with controlled nausea or vomiting. This is a 30% increase in cost per month.

Pathophysiology of CINV

The pathophysiology of CINV is not entirely understood, however it is thought to have many contributing pathways. Vomiting or emesis occurs when the vomiting center (VC), located in the medulla near the respiratory center on the floor of the fourth ventricle, is activated. Activation of the VC can arise from pathways in the gastrointestinal (GI) tract, chemoreceptor trigger zone (CTZ), vestibular apparatus, cerebral cortex or a combination of these pathways (Camp-Sorrell, 2005). The VC is sensitive to several neurotransmitters that are released through each pathway. Activation from the vestibular-cerebellar pathway, a result of motion sickness or when rapid changes in motion occur, is not directly involved in CINV.

The two pathways thought to be directly involved with CINV are the GI tract and the CTZ. When rapidly dividing enterochromaffin cells located in the GI tract are damaged, serotonin is released and binds to vagal afferent receptors that stimulate emesis through the CTZ or directly through the VC. The CTZ is a highly vascular organ that is not confined to the blood-brain barrier and is therefore vulnerable to exposure to chemotherapy from the blood as well as cerebral spinal fluid (Wickham, 2004). The CTZ is located in the area postrema and is near the VC.

Activation of the VC directly or through the CTZ results in stimulation of the salivation and respiratory centers as well as control of the pharyngeal, GI and abdominal muscles. The neurotransmitters most responsible for the activation of the CTZ in CINV are serotonin and substance P. Noradrenaline, somatostatin, enkephalin, acetylcholine, aminobutyric acid, vasopressin and cortisol can also induced vomiting through the CTZ. Though the VC has many neurotransmitter receptors it is most sensitive to muscarinic and dopamine (Murphy-Ende, 2006).

Research has primarily focused on the pathophysiology of acute and delayed CINV, thus the pathophysiology of nausea as a sole entity is less known. It is thought that nausea is mediated by the autonomic nervous system. The CTZ is also felt to be more greatly involved in nausea than in vomiting (Murphy-Ende, 2004).

Clinical Presentation

Nausea can be described as an unpleasant or queasy feeling causing a desire to vomit. It is important to note that nausea is not always accompanied by vomiting. The act of vomiting can be defined as the expulsion of gastric content through the mouth (Camp-Sorrell & Hawkins, 2006, chap. 60). Clinical manifestations that may accompany nausea include tachycardia, perspiration, light-headedness, dizziness, pallor, excess salivation, anorexia and weakness.

Differential Diagnosis

Nausea and vomiting in cancer patients can be multi-factorial. Evaluation of symptoms should reflect this. Nausea and vomiting can have structural, psychological, chemical, metabolic or a combination of origins. When evaluating cancer patients with suspected CINV, causes such as pain, anxiety, hepatosplenomegaly, bowel obstruction, metastasis or increased ICP should also be considered. Immunocompromised and elderly patients should also be evaluated for bacterial or viral gastroenteritis as these populations may be more vulnerable to an infectious process. It is crucial to illicit onset and duration as well as any potential associated, aggravating or relieving symptoms.

Differential Diagnoses	
Structural: Bowel Obstruction Hepatosplenomegaly Brain metastasis	Psychological: Anxiety Depression Uncontrolled pain
Chemical: Opioids Antidepressants Antibiotics	Metabolic: Hypo/Hyponatremia Hypo/Hyperkalemia Hypercalcemia

Relevance to Oncology Nurses

Oncology nurses possess the ability to educate patients undergoing potentially emetogenic therapy regarding possible risks and risk modifications, non-pharmacologic treatment and potential side effects from prescribed antiemetics. Assessment, communication and education are key nursing roles in the successful treatment of CINV. Kearney et al. (2008) reports that symptom outcomes for nausea and vomiting were significantly improved utilizing a program that incorporated patient-reported symptoms using an electronic tool and nursing management guided by evidenced-based practice protocols.

Greater than 76% of physicians and 80% of nurses underestimated the incidence of delayed CINV (Grunberg et al., 2004). These startling statistics emphasize the importance of accurate assessment and communication. Oncology nurses should complete a thorough history, review of systems and physical exam. Past medical history should include cancer diagnosis and all past and current medical conditions. Review of systems assessment should include all body systems as this can narrow the field of differential diagnoses. Focused nursing physical assessment should include vital signs, evaluation for orthostatic hypotension, assessment of fluid status (measuring output, assessing for edema and monitoring daily weights), pain, manifestations of

electrolyte imbalance (malaise, fatigue, weakness, palpitations, paresthesias or muscle cramps) and manifestations of metabolic alkalosis (impaired mentation, hypotension or hypoventilation). Assessment for viral symptoms (myalgias, arthralgias, rhinorrhea, headache, stiff neck, vertigo, tinnitus, chest pain, cough and fever) as well as neurologic and vestibular symptoms must also be evaluated. Metastatic brain lesions may cause increased intracranial pressure resulting in acute nausea, vomiting or headache. These symptoms coupled with change in motor or sensory function, personality change or seizures should be evaluated immediately.

Evidence-Based Management Plan

Recent advances in medications have increased the number of highly effective agents available to treat CINV. 5-Hydroxytryptamine₃ (5-HT₃) serotonin receptor antagonists include: dolasetron, granisetron, ondansetron and palonosetron. These agents work by binding to 5-HT₃ receptors both in the peripheral and central nervous system, thus preventing the activation of the CTZ. Although efficacy has proven to be similar with 5-HT₃ serotonin receptor antagonists (Hawkins & Grunberg, 2009), palonosetron is favorable in some clinical situations because of its long half-life (approximately 40 hours) and minimal toxicity profile. 5-HT₃ serotonin receptor agonists are used to prevent acute CINV and are available in oral or intravenous preparations.

Neurokinin 1 (NK1) receptor antagonists are used for delayed CINV and work by binding to the NK1 receptor and blocking substance P. Currently fosaprepitant can be administered intravenously on day one of treatment followed by two additional days of oral therapy (aprepitant) or orally for 3 days. Corticosteroids, methylprednisone or dexamethasone, can be used as single agents or in combinations with 5-HT₃ serotonin receptor antagonists and/or NK1 receptor antagonists. The mechanism by which corticosteroids decrease CINV has yet to be determined; however multiple clinical trials have demonstrated improved outcomes when corticosteroids are used in antiemetic regimens (Musso et al., 2009; Grunberg et al., 2008).

Metoclopramide, compazine and cannabinoids are recommended only when a patient is experiencing CINV which is refractory to 5-HT₃ and/or NK1 (Kris et al., 2006). Adjunctive agents such as benzodiazepines and antihistamines may be helpful adjuncts to antiemetic therapy however Kris et al. do not recommend their use as single agents. Benzodiazepines may be beneficial in patients experiencing anticipatory nausea. Benzodiazepines can be taken orally prior to chemotherapy treatment to reduce anticipatory nausea.

Antiemetic Therapies

5-HT₃ Antagonists

- dolasetron
- granisetron
- ondansetron
- palonosetron
- tropisetron (not avail in US)

NK₁ Receptor Antagonists

- aprepitant (oral formulation)
- fosaprepitant (IV formulation)

Corticosteroids

- dexamethasone
- methylprednisone

Miscellaneous Agents

- metoclopramide
- compazine
- cannabinoids
- benzodiazepines
- antihistamines

Treatment Guidelines

Several guidelines exist that clearly delineate the prevention and treatment of CINV. Perhaps the most commonly referred to published guidelines include those from the American Society of Clinical Oncology (ASCO), the Oncology Nursing Society (ONS) and the National Comprehensive Cancer Network (NCCN) guidelines. Adherence to the approved guidelines is essential for improved CINV outcomes. Ihbe-Heffinger et al. (2004) found that more than 50% of patients were treated with a prophylactic regimen that was not in agreement with the ASCO guidelines and a significantly higher proportion of these undertreated patients experienced delayed CINV than appropriately treated patients. In order to effectively prevent and treat CINV the level of emetogenic potential needs to be correctly identified.

Chemotherapies that are considered highly emetogenic (HEC) have a greater than 90% incidence of CINV and include cisplatin, mechlorethamine, streptozocin, cyclophosphamide (greater than 1,500 mg/m²); moderately emetogenic chemotherapies (MEC) include treatments with a 30%-90% incidence and include oxaliplatin, cytarabine (greater than 1 Gm/m²), carboplatin, ifosfamide, doxorubicin, daunorubicin, epirubicin, idarubicin and irinotecan. Paclitaxel, docetaxel, mitoxantrone, etoposide, pemetrexed, methotrexate, mitomycin C, gemcitabine, cytarabine (less than 100mg/m²), 5-fluorouracil, bortezomib, cetuximab and trastuzumab have a 10%-30% incidence of CINV and are considered low-risk regimens (Grunberg, 2007).

The three guidelines are very similar for the prevention of CINV with HEC. NCCN, ONS and ASCO agree that acute CINV should be prevented with a 5-HT₃ antagonist with dexamethasone and aprepitant and/or lorazepam. Guidelines for the prevention of delayed nausea in HEC are very similar as well and include dexamethasone and aprepitant on days 2 and 3 of the chemotherapy cycle (Kris et al., 2006, Tipton et al.,

2007, NCCN, 2008). ONS and NCCN guidelines also include lorazepam as possible treatment of delayed nausea (Tipton et al, NCCN).

The guidelines for the prevention of CINV with MEC vary slightly. ONS and NCCN agree that for prevention of acute CINV a 5-HT3 antagonist, dexamethasone and aprepitant with or without lorazepam should be given, while the ASCO guidelines simply advise use of 5-HT3 antagonist with dexamethasone (Kris et al., Tipton et al., NCCN). Delayed CINV prevention guidelines for MEC differ as well. ONS recommends that aprepitant be used in combination with either dexamethasone, 5-HT3 antagonist, metoclopramide and/or diphenhydramine on days 2 and 3 of chemotherapy; in contrast NCCN does not include metoclopramide or diphenhydramine in the suggested treatment of delayed CINV (Tipton et al., NCCN). The ASCO guidelines state that delayed CINV should be prevented with dexamethasone or 5-HT3 antagonist on days 2-3, with the exception that any persons receiving cyclophosphamide plus anthracycline should receive antiemetic protection as HEC risk (Kris et al.).

According to ASCO guidelines persons receiving LEC only require dexamethasone prior to treatment while in contrast ONS guidelines do not recommend an antiemetic or any of the following: dexamethasone, prochlorperazine, metoclopramide or lorazepam. NCCN guidelines for LEC are similar to those from ONS with the potential to include diphenhydramine if desired (Kris et al., Tipton et al., NCCN). ASCO, ONS and NCCN guidelines do not recommend prophylactic antiemetics for chemotherapy regimens with emetogenic potential less than 10%.

Conclusion

Acute, delayed, anticipatory and breakthrough nausea continue to negatively impact the QOL of patients receiving cancer therapies. It is absolutely essential that health care providers accurately acknowledge and treat this issue. In order to improve patient outcomes, health care providers must become familiar with and follow clinical practice guidelines, as well as current evidenced-based information. In the future additional research in non-pharmaceutical interventions would be useful. Evidence has shown that hypnosis can effectively treat anticipatory CINV (Richardson et al., 2007) and early research indicates that alternative treatments such as acupuncture and massage may also be beneficial in prevention of CINV. As new cancer therapies become available it is crucial to manage symptoms effectively for benefit of patients.

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