Optimizing Antiemetic Therapy for Chemotherapy-induced Nausea and Vomiting

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Learning Objectives
Upon completion of this program the participant will be able to:
1. Identify the types and pattern of CINV.
2. Describe the pathophysiology of CINV.
3. Identify the emetogenic potential classification of individual chemotherapy agents.
4. Prescribe antiemetic therapy based upon the emetogenic potential of the chemotherapy.
5. Describe the rationale for implementing prescribing guidelines for antiemetic therapy for CINV.

Abstract: Patients receiving chemotherapy cite chemotherapy-induced nausea and vomiting (CINV) as the symptom causing the most concern. The symptoms vary from slight nausea to protracted vomiting with subsequent dehydration. While recent progress has been remarkable, CINV continues to be an important problem since many patients experience this side effect.

The pathophysiology of CINV is not well understood, but serotonin (5-HT_3) receptors play an apparent important role. However, many other pathways are probably involved in CINV, and a combination of agents may be necessary to prevent nausea.

The types and pattern of CINV are acute, delayed, and anticipatory nausea and vomiting. The acute and delayed phases of CINV are unique to the chemotherapy agents administered. An understanding of each of these phases of CINV enables the pharmacist to make prescribing recommendations.

Each chemotherapy agent will demonstrate different levels of emetogenic potential. Classification of the agents in a systematic manner is an important tool for guiding the selection of antiemetics. The high and moderately emetogenic chemotherapy agents will require corticosteroid and serotonin antagonists to prevent nausea.

Prescribing antiemetics according to practice guidelines can improve outcomes of patients and reduce the cost of therapy. A methodology to provide consistent antiemetic therapy for patients receiving chemotherapy is a necessary to provide the best care for cancer patients.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) has been cited by patients as the symptom causing the most concern when receiving chemotherapy.[1] The symptoms vary from slight nausea to protracted vomiting with subsequent dehydration. Studies have demonstrated that nausea and vomiting seriously impacts a patient's quality of life.[2] While recent progress has been remarkable, chemotherapy-induced emesis continues to be an important problem since many patients experience this side effect.[3] Prevention of nausea and vomiting induced by chemotherapy continues to challenge the oncologist, pharmacist, and nurse.

Chemotherapy-induced nausea and vomiting (CINV) is a significant adverse side effect for patients receiving chemotherapy. Patients treated with chemotherapy may experience anticipatory, acute, and delayed nausea and vomiting. The choice of antiemetic therapy is a vital part of preventing these symptoms and enhancing patient satisfaction. In addition, consideration of the emetogenic potential of chemotherapy agents is important for appropriate prescribing of antiemetics. This program will review the pathophysiology of CINV, antiemetic pharmacology, and appropriate guidelines for prophylaxis of CINV.

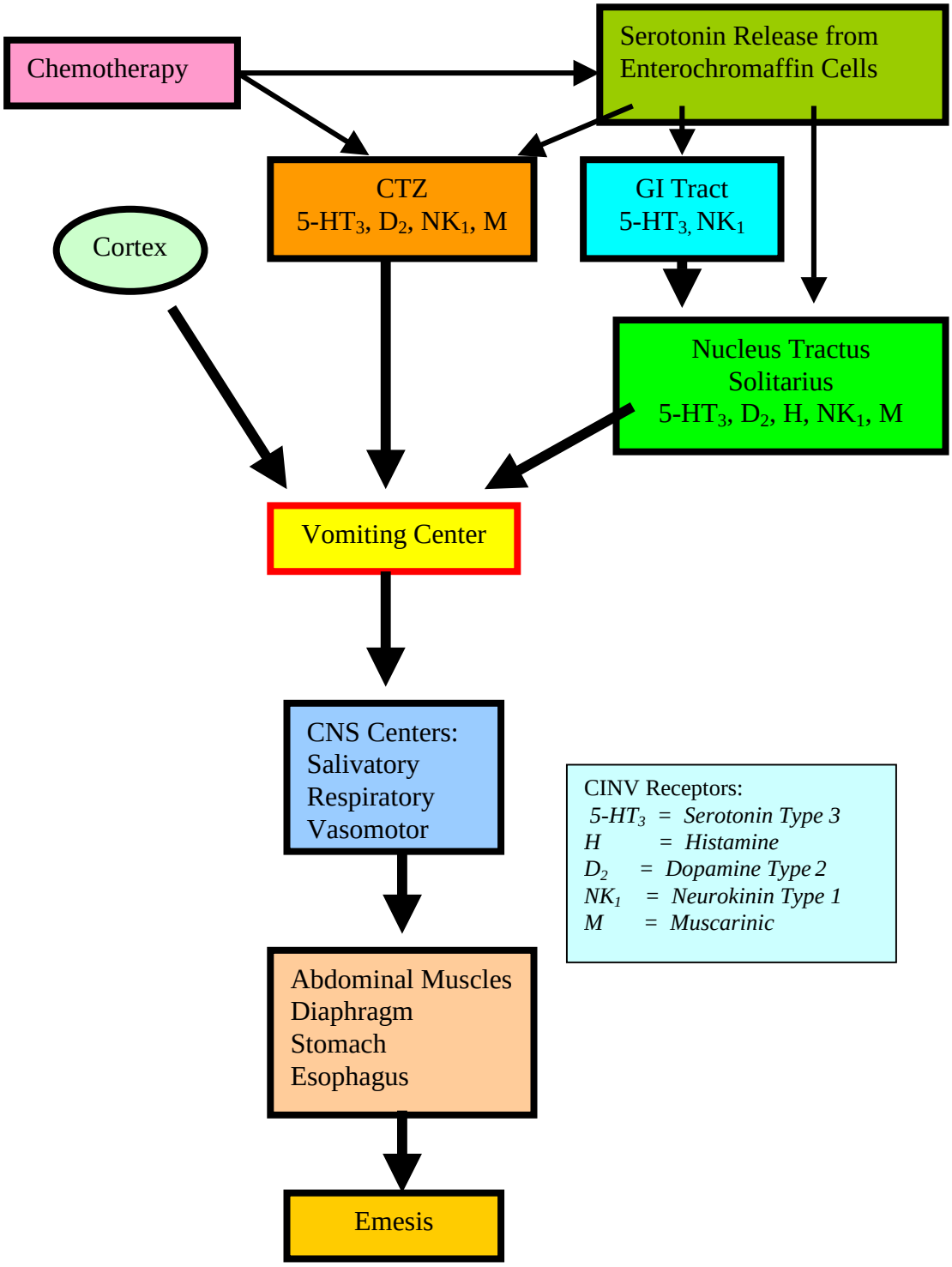
Pathophysiology of Chemotherapy-induced Nausea and Vomiting

The vomiting or emetic center (VC) is the physiologic control center causing emesis and is located in the lateral reticular formation of the medulla in the brain. It receives input from several areas including the nucleus tractus solitarius, the chemoreceptor trigger zone, the vestibular system, and the gastrointestinal (GI) tract. The emetic process is initiated by the stimulation of dopamine, opiate, histamine, acetylcholine, neurokinin 1, or serotonin type-3 (5-HT_3) receptors. The exact mechanism for CINV remains unclear. But studies demonstrate the importance of dopamine type 2 (D_2) and serotonin in the mechanism. Chemotherapy stimulates the release of serotonin from the enterochromaffin cells lining the GI tract. The serotonin stimulates type-3 vagal afferent serotonin receptors (5-HT_3) located in the GI tract, the nucleus tractus solitarius (NTS) of the medulla oblongata, and the chemoreceptor trigger zone (CTZ). The CTZ lies outside the blood-brain barrier and sends impulses to the vomiting center when stimulated by an emetogenic substance.[4] The physiologic mechanism for chemotherapy-induced nausea and vomiting has been hypothesized to follow this sequence of events (see Figure 1):

1. Chemotherapy stimulates the CTZ directly.
2. Chemotherapy stimulates enterochromaffin cells in the GI tract to release serotonin.
3. Serotonin activates 5-HT_3 receptors in 3 areas: vagal afferents in the GI tract, NTS, and the CTZ.

4. Dopamine-2, histamine, and neurokinin-1 receptors are stimulated.
5. Impulses feed into the VC.
6. When a threshold is reached in the VC, nerve impulses are carried by efferent nerves to stimulate emesis.

Figure 1. Responsible Neurotransmission Pathways for CINV[4]



Pattern of Chemotherapy-induced Nausea and Vomiting

CINV is classified by the pattern and time in which it occurs. The 3 patterns occurring in oncology patients are acute, delayed, and anticipatory nausea and vomiting (Figure 2).

Acute Nausea and Vomiting

Acute nausea and vomiting is arbitrarily defined to occur within 24 hours of administration of emetogenic chemotherapy. The neurophysiology of acute CINV is complex. The type of chemotherapy as well as the dose and administration has an impact on the severity or risk of acute emesis. While serotonin antagonists have reduced the severity of this phase of CINV, other yet to be discovered mechanisms have been implicated. There are many variables that should be considered. Patient-specific factors play an important role in predicting the risk for CINV.[4] Patients younger than 50 years old and women are more likely to experience CINV. Older patients, men, and those that drink large quantities of alcohol are less likely to experience CINV. Obtaining an accurate patient history is an important component of determining the likelihood of emesis in a given patient.

Cisplatin in doses of 50-120mg/m_2 will cause emesis in the majority of patients within 24 hours of administration.[5] Cisplatin has a peak emetogenic effect at approximately 4 hours after administration during the acute phase of nausea.[6] The release of serotonin from the enterochromaffin cells has been demonstrated with the administration of cisplatin.[7] A peak in urinary metabolites of serotonin (5-HIAA) occurs 6 hours after cisplatin administration suggesting a strong correlation of serotonin release and vomiting with this agent.[8] High-dose cyclophosphamide causes a peak emetogenic effect approximately 10-12 hours after administration, and can last up to 3 days. This may be because of the conversion of the cyclophosphamide to metabolites that have emetogenic properties.[4] Mechlorethamine induces emesis within 30 minutes of administration suggesting that this agent has a direct ability to stimulate emetic centers, while most other agents have a peak emetic effect within 6 hours.[4] Excluding patient variability, the degree of acute nausea is influenced by the type of agent, dose, and rate of infusion.[4]

It is important to consider that each chemotherapy agent has different emetogenic properties. Emetogenicity is the potential of a chemotherapy agent to produce emesis in a patient receiving that particular agent. Researchers have classified the emetogenic potential of chemotherapy agents (Table 1).[9] For instance, vincristine and vinorelbine have very low potential for producing acute emesis. However, carmustine and dacarbazine have a very high risk for producing emesis. This should influence prescribing of antiemetics to prevent CINV as we will discuss later.

Delayed Emesis

Delayed emesis occurs 24 hours or more after chemotherapy has been administered. This effect can be can be observed for as many as 5 days after treatment. Cisplatin causes the most severe delayed emesis.[10] However, cyclophosphamide, carboplatin, and anthracyclines are also responsible for this delayed effect. The mechanism of delayed emesis is not clearly understood and is, most likely, mutifactorial.[11]

Anticipatory Emesis

This is nausea or vomiting that may begin because of the environment even before the chemotherapy is administered. It is associated with poor emesis control with prior treatments. A patient that has experienced emesis from past treatments is "conditioned" to respond to the environmental stimuli. Therefore, patients may experience nausea when they see the doctor, nurse, or treatment area that was associated with the past history of emesis.

Prevention of Acute Chemotherapy-induced Nausea and Vomiting

The acute phase of CINV offers the clinician the greatest opportunity for improving the outcomes of a patient's care. Cisplatin has a history of causing profound nausea and vomiting that is difficult to prevent. Therefore, cisplatin has become the benchmark agent to test new antiemetics for activity against CINV. The serotonin antagonists have the most significant activity in the treatment of acute nausea and vomiting associated with cisplatin.[12] The serotonin antagonists block 5-HT_3 receptors in the CNS as well as the vagal periphery resulting in significant reductions of acute nausea induced by chemotherapy.[13] Stimulation of the CTZ also plays a significant role in the pathogenesis of CINV. The CTZ can be stimulated by emetogenic substances either in the blood or the cerebrospinal fluid. Stimulation of D_2 receptors, opioid receptors, and 5-HT_3 receptors has been cited as the possible mechanism for CTZ-mediated nausea and vomiting. Input from the CTZ transmits directly into the VC, which, in turn, causes neuronal activity in the periphery resulting in vomiting. Therefore, D_2 antagonists, such as the phenothiazines and butyrophenones, have demonstrated limited activity in preventing acute CINV. They have shown some added benefit as treatment for breathrough nausea and vomiting when patients are already receiving dexamethasone and serotonin antagonists for CINV.

When prescribing antiemetics for acute CINV, it is important to consider the emetogenic potential of the chemotherapy. Emetogenic potential is defined as the intrinsic capacity of a chemotherapy agent to produce an emetic episode in a patient receiving the agent. The evaluation and classification of the emetogenic potential of chemotherapy agents can enable the clinician to choose appropriate interventions that are cost-effective. This method provides a cost-effective tool to prevent nausea and vomiting in patients treated with chemotherapy. The emetogenic potential of chemotherapy agents varies widely based on the agent and dose administered. The appropriate antiemetic can be selected based on the classification of the chemotherapy being administered. Emetogenic classification provides a tool for predicting the incidence of CINV prior to prescribing and treatment, accordingly.

Chemotherapy agents have been classified as having either a very high, high, moderate, low, or very low emetogenic potential as shown in Table 1.[14] Agents such as paclitaxel (Taxol), vinorelbine, and vincristine have low emetogenic potentials requiring minimal antiemetic intervention as needed. The use of a phenothiazine such as prochlorperazine should be adequate for prevention of nausea and vomiting. Chemotherapy agents such as idarubicin and mitomycin have a slightly higher incidence of nausea requiring scheduled dexamethasone with or without other agents to prevent nausea and vomiting. This will prevent nausea and vomiting in most cases without using the more expensive serotonin antagonists. The chemotherapy agents that have a high (level 4) emetic potential include agents such as carmustine, ifosfamide, and high doses of doxorubicin. Agents such as high-dose cisplatin and streptozocin have a very high

(level 5) emetogenic potential. Chemotherapy agents classified as level 4 or 5 require aggressive antiemetic treatment because of the high incidence of emesis (>60%). The agents with highly emetogenic properties are treated with dexamethasone 20 mg and serotonin antagonists (doses are listed in Table 2) before the chemotherapy is administered.

Combinations of agents with moderate emetogenic potential will sometimes produce a higher than expected incidence of nausea and vomiting because of additive effects. The combination of cyclophosphamide, doxorubicin, and fluorouracil has a slightly higher potential for causing emesis than each has as a single agent.[10] However, the best approach for preventing CINV is to treat according to the most highly emetogenic agent. In addition, when agents that normally have low or moderate potential are given in high doses, such as those administered in bone marrow transplantation, aggressive treatment with antiemetics prescribed for breakthrough nausea may be necessary to prevent nausea and vomiting.

A wide selection of antiemetic is available to treat CINV. Table 2 lists the choices with the suggested doses of each agent.

Metoclopramide Use in Acute CINV

Prior to the introduction of serotonin antagonists, high-dose metoclopramide was frequently used. High doses of metoclopramide for CINV ranged from 1-2 mg/kg, and were repeated as often as every 3 hours with a maximum dose of 12 mg/kg/day. It was the mainstay of treatment for the prevention of emesis when administering highly emetogenic agents until serotonin antagonists became available. About 10% of patients receiving metoclopramide can experience CNS side effects including sedation and extrapyramidal symptoms and sedation. Dystonic reactions can be as high as 25% in younger patients.[15] These undesirable adverse effects, although ameliorated by diphenhydramine, motivated researchers to find an agent that had the same antiemetic properties but with less severe adverse effects.

Serotonin Antagonists in Acute CINV

Serotonin antagonists have greatly enhanced the clinician's choices for treatment of CINV. Currently, ondansetron, granisetron, and dolasetron are available as choices. The side effect profile is similar for all of these agents. Headache is the most common side effect, followed by an asymptomatic prolongation of electrocardiographic interval.[4]

Ondansetron

The development of ondansetron represented a significant improvement as an agent to treat CINV. Ondansetron was found to have a more specific blockade of the serotonin receptor site than metoclopramide, but with fewer adverse effects. Several studies comparing efficacy have shown superiority of intravenous ondansetron over intravenous high-dose metoclopramide.[13,16,17] It has a better side effect profile than metoclopramide, with headaches being the only major side effect experienced. Determining the most effective doses of serotonin antagonists for various chemotherapy regimens has been an important issue in treatment because of the high cost of these antiemetic agents. The package insert promotes the use of ondansetron 32 mg. The information found in the literature offers insight for the clinician that desires to prescribe these medications in a cost-effective manner.

A United States study by Beck demonstrated that ondansetron 32 mg had a significantly greater response rate than either a single 8 mg dose or 0.15 mg/kg times 3 doses ($P = 0.048$).[18] In an early dose-finding study in patients receiving cisplatin, intravenous ondansetron doses ranging from 0.01 mg/kg to 0.48 mg/kg were compared. The investigators found that doses above 0.36 mg/kg offered no greater efficacy but had an increased incidence of headaches.[19] In a 70-kg patient, this dose approximately equals 25 mg. In a European study in 496 patients comparing once daily intravenous doses of ondansetron 32 mg, ondansetron 8 mg, and granisetron 3 mg, the investigators found no significant difference in the three arms.[20] This study demonstrated the efficacy of low doses of ondansetron in patients receiving chemotherapy. Some centers have reported that 20 mg of ondansetron is effective when combined with dexamethasone for cisplatin-induced nausea and vomiting.[21] Lower doses of ondansetron appear to be equally effective. A study in 973 patients comparing ondansetron 8 mg IV to granisetron 3 mg showed no significant difference in preventing cisplatin-induced nausea.[22] In a study by Hesketh et al., ondansetron was dosed according to emetogenic potential of the agents prescribed. Patients received either 8, 24, or 32 mg of drug depending upon whether they received high (cisplatin > 70 mg/m^2), moderately high (cisplatin 20-70 mg/m^2), or moderately (no cisplatin or < 20mg/m^2) emetogenic chemotherapy. The investigators observed a complete response in 77%, 88%, and 72% in the patients receiving 8-, 24-, and 32-mg arms, respectively. The study concluded that when combined with a fixed dose of dexamethasone, lower doses of ondansetron are effective for chemotherapy with moderately high emetogenic potential.[23]

A consensus of researchers has assigned a high level of support for a dose of 8 mg intravenously or 0.15 mg/kg as a one-time dose before moderately high, high, or very highly emetic chemotherapy in adult patients.[24] FDA-approved doses for ondansetron range from 8-32 mg intravenous or 8-24 mg orally to prevent CINV.

Granisetron

Granisetron is a serotonin antagonist used extensively in Europe before introduction in the United States. The standard intravenous dose of granisetron in Europe is 3 mg or 40 mcg/kg/day. Noble et al. compared granisetron 3 mg IV once daily and ondansetron 8 mg IV 3 times daily in a double-blinded, crossover study. The investigators found no significant difference in response or failure in patients receiving 5 days of chemotherapy consisting of cisplatin 15 mg/m^2 or ifosfamide 1.2 g/m^2 daily in combination with other agents.[25] Gebbia et al. compared intravenous granisetron 3 mg and intravenous ondansetron 24 mg on day 1 of cisplatin therapy and found no significant difference in response.[26] This study also tested the effects of both agents on delayed effects of cisplatin demonstrating that neither had very little benefit against delayed nausea and vomiting. Ruff et al. compared intravenous granisetron 3 mg with intravenous ondansetron 8 mg and 32 mg as a single dose for the prevention of cisplatin-induced CINV in a total of 496 patients. No statistical difference in response was found in the treatment arms.[20] Jantunen et al. studied the use of intravenous doses of ondansetron 8 mg, tropisetron 5 mg, and granisetron 3 mg in 166 patients receiving moderately emetogenic chemotherapy with similar efficacy of all 3 agents.[27] Granisetron has proven to be effective in the treatment of CINV when given as a once daily dose. Studies in the ferret model suggest that granisetron has twice the duration of action of ondansetron possibly because of binding affinity to 5-HT$_3$ receptor

sites.[28] Granisetron shares some of the same dosing confusion that is seen with ondansetron. When approved for use in Europe, granisetron was given intravenously as 40 mcg/kg once daily. This represents an average of 3 mg of granisetron per day. A significant number of studies were performed in Europe at the 3-mg intravenous dose. While the Europeans have used 40 mcg/kg once daily as an approved dose, the United States-approved daily intravenous dose is 10 mcg/kg of granisetron. Studies have shown that no significant difference exists between 10 mcg/kg or 40 mcg/kg of granisetron.[29,30] Studies that evaluated the efficacy of oral granisetron concluded that 2 mg given either as a single dose or divided into 2 doses daily is effective for highly emetogenic chemotherapy. [31,32] A consensus of researchers has supported the use of either granisetron 1 mg intravenously or 2 mg orally in adult patients for high or very highly emetic chemotherapy.[24]

Dolasetron

Studies with dolasetron have shown similar effectiveness to ondansetron for prevention of the acute phase of CINV.[33,34] Dolasetron also has comparable activity to granisetron when given in doses of 1.8 mg/kg intravenously.[35] Dolasetron has had numerous studies to determine the most effective dose. Hesketh and colleagues compared dolasetron 1.8 mg/kg and 2.4 mg/kg intravenously to ondansetron 32 mg intravenously in 609 patients receiving cisplatin. The results indicated that dolasetron 1.8 mg/kg intravenously is equally effective as ondansetron.[33] A pooled analysis of trials demonstrates that a dose rounded to 100 mg intravenously is adequate for prevention of CINV.[36] Research comparing 4 oral doses of dolasetron in moderately emetogenic chemotherapy supports the use of dolasetron 100 mg orally.[37] A consensus of researchers confirms the use of dolasetron 100 mg intravenously or 100 mg orally in preventing CINV in adult patients.[24]

Corticosteroid Use in Acute CINV

Dexamethasone was found to improve efficacy when added to metoclopramide, so researchers tested it in combination with ondansetron. Its mechanism of action is not understood. When dexamethasone is added to ondansetron, there is a significant improved response. A study by Roila et al. revealed that by combining dexamethasone with ondansetron the antiemetic response was improved by as much as 27%.[38] The increased efficacy of the serotonin antagonists when combined with dexamethasone makes this combination a standard of treatment unless contraindicated. Patients may experience short-term hyperglycemia with the administration of dexamethasone. In addition, immunosuppression and adrenal suppression can occur when corticosteroids are used for a prolonged period. If intravenous dexamethasone is given too rapidly, the patient may experience perineal burning, but is minimized by administering the 20 mg dose over at least 20 minutes.

Other Agents Used in Acute CINV

Butyrophenones and phenothiazines are useful for breakthrough nausea when patients fail standard therapy. They are not indicated as first-line therapy for highly emetogenic chemotherapy except in combination with serotonin antagonists. They offer the greatest benefit to prevent CINV mediated by the CTZ center. The recommended dose of the butyrophenone, droperidol (Inapsine®), is 1.25 mg to 2.5 mg intravenously every 4 to 6 hours. The adult dose for the phenothiazine, prochlorperazine (Compazine®), is 5-20 mg orally or intravenously every

6 to 8 hours in adults up to 40 mg per day. These agents can cause sedation as well as extrapyramidal effects in normal doses.[39]

In summary, the prevention of acute nausea and vomiting is best managed by the use of dexamethasone in combination with serotonin antagonists. Therapeutic doses for each of these agents are listed in Table 2. Other agents, such as metoclopramide, prochlorperazine, or droperidol should be added for breakthrough nausea. If nausea and vomiting are experienced for more than 24 hours after chemotherapy, treatment options should follow the schema for delayed nausea and vomiting.

Prevention of Delayed Nausea and Vomiting

Delayed emesis presents the greatest challenge to the clinician. The etiology of delayed nausea and vomiting is caused by mechanisms that are not well understood. Several hypotheses for delayed emesis have been suggested including drug metabolites or cell death by-products, which stimulate sites responsible for emesis. Agents such as cisplatin, cyclophosphamide, doxorubicin, and carboplatin exhibit a consistent delayed emesis effect, with cisplatin being the worst. Some chemotherapy agents can cause an escalating degree of nausea when given over several days or in high doses. This is especially seen during the later phases of multi-day, high-dose chemotherapy. Substance P action on neurokinin-1 receptors may also be partly responsible, since investigators have found promising results with NK-1 antagonists in preventing cisplatin- induced delayed nausea and vomiting.[40,41] Delayed nausea and vomiting is most likely caused by multifactorial causes, and will require further research to completely understand.

Delayed nausea and vomiting from chemotherapy is a symptom that is not easily treated. The delayed emetic effect has an onset more than 24 hours after chemotherapy administration. Therefore, the patient receiving these agents will require antiemetic treatment beyond the first 24 hours to reduce nausea and vomiting. Cisplatin has the most pronounced delayed effect of nausea and vomiting, and is the basis for study of this phenomenon.

Corticosteroids, such as dexamethasone, have an unknown mechanism of action but have been shown, thus far, to have the best effectiveness against delayed emesis. A study by Kris et al. compared oral administration of placebo, dexamethasone, and a combination of metoclopramide plus dexamethasone. The combination of metoclopramide 0.5 mg/kg 4 times daily for 4 days plus dexamethasone 8 mg twice daily for 2 days then 4 mg twice daily for 2 days had significantly better control of delayed emesis.[42] The use of oral dexamethasone plus metoclopramide has been given a high level of support for reduction of delayed emesis because of cisplatin.[24]

Serotonin may also play a role in delayed nausea and vomiting since some investigators have demonstrated partial responses from serotonin antagonists.[43] However, Gandara et al.[44] and Kris et al.[45] studied the use of oral ondansetron for delayed emesis and found no significant advantage over placebo. Another study of delayed emesis by the Italian Group for Antiemetic Research with 618 patients demonstrated no significant difference between oral dexamethasone 4 mg BID compared with oral dexamethasone 4 mg BID plus oral ondansetron 8 mg BID.[46] Prescribing serotonin antagonists for delayed emesis is not clearly demonstrated by the literature.

A consensus of researchers agrees that a corticosteroid, in combination with metoclopramide or serotonin antagonists is necessary to ameliorate delayed emesis for cisplatin regimens. They also recommend that corticosteroid alone may be adequate for non-cisplatin regimens with the option of adding metoclopramide.[24,47]

Prevention of Anticipatory Nausea

The cerebral cortex plays an important role in nausea and vomiting that is complex and difficult to predict. Stored memories in the cortex are responsible for the anticipatory nausea associated with chemotherapy. The conditioned response is "remembered," and can be complicated by anxiety associated with the treatment. Treatment with anxiolytics such as lorazepam are beneficial for this type of nausea. Previous experience will play into the incidence of this type of nausea and vomiting. Therefore, the incidence can be decreased by effective prevention of acute and delayed nausea and vomiting.

Development of Practice Guidelines for CINV

Developing practice guidelines is a way of providing a systematic method to provide cost-effective ways to prevent CINV. Clinical practice guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for a clinical circumstance."[48] By the use of practice guidelines, consistent prescribing allows for assessment to determine cost-effectiveness of a given treatment. Cost-effectiveness can be defined by the apparent value or outcome obtained with consideration given to the cost to achieve that outcome. Employing practice guidelines should enhance therapy by continuously assessing and adjusting therapy. When considering which antiemetic to prescribe, the cost of the agent should be considered. The serotonin antagonists, dolasetron, ondansetron, and granisetron represent the most costly agents. Therefore, they should be used judiciously to prevent unnecessary expense. Using the oral route for each of these agents reduces the cost of treatment. For example, granisetron 1-mg intravenous could cost as much as $166.00, while the 2-mg oral tablets cost $78.00. The appropriate prescribing of the most cost-effective agent, route, and dose can have a significant impact on the drug expense for the hospital or clinic. It should also prevent the use of a $100.00 drug when a $2.00 drug would result in the same effect or outcome. After implementation of practice guidelines for treatment of CINV, Berard and Mahoney reported savings of 32% to 38% over previous expenses on serotonin antagonists.[49]

The following recommendations should be implemented into guidelines:[4]

1. The emetic potential should be considered when deciding which antiemetics should be prescribed.
2. When chemotherapy agents are assigned emetogenic levels 2-5, an antiemetic should be prescribed each day the chemotherapy is given.
3. Patients receiving chemotherapy with a classification of emetogenic levels 3-5 should be given dexamethasone and a serotonin antagonist.
4. Oral serotonin antagonists are considered equivalent to intravenous if they are given at least 30 minutes in advance of chemotherapy administration. The decision to use an oral or intravenous route will be patient-specific.

5. Deciding which serotonin antagonist to use can be based on the cost of equivalent therapeutic doses of the agents. An equivalent dose of any of the serotonin antagonists can be used (see Table 2).
6. All patients will need the availability of antiemetics for rescue of breakthrough nausea and vomiting. It is important that the patient is educated on the appropriate administration and side effects of these medications. In adults, lorazepam, prochlorperazine, metoclopramide, dexamethasone, haloperidol, and dronabinol are effective. The choice of agents should be based on patient-specific success, adverse effects, and cost (see Table 3).
7. To prevent delayed emesis resulting from cisplatin therapy in adults, dexamethasone and metoclopramide or a serotonin antagonist is recommended. For adults receiving non-cisplatin agents causing delayed nausea, dexamethasone by itself or with metoclopramide or serotonin antagonists is recommended.

Tables 1, 2, 4, and 5 are representative of simple guidelines that could be used to deliver antiemetics in a cost-effective manner. Table 4 provides recommended treatment guidelines for CINV for very high (Level 5), high (Level 4), moderate (Level 3), and low (Level 2) emetogenic potential. Table 5 provides guidelines for treating delayed emesis from chemotherapy. Clinicians should first determine the emetogenic potential of the chemotherapy and then prescribe according to guidelines. As outcome data is collected, assessment and changes can be made to improve the effectiveness of these guidelines.

The formation of practice guidelines for CINV should include the following:

- The emetogenic potential of the chemotherapy should be evaluated by current literature and classified.
- The serotonin antagonist of choice based on the best cost-effectiveness should be designated for those patients with high to moderately high emetogenic chemotherapy in combination with dexamethasone.
- The dose and route should be chosen that represent the most cost-effective benefit to the patient.
- Results of treatment should be documented for each patient. This approach will improve the outcome of patients receiving chemotherapy and allow reduction of costs associated with the treatment of CINV.

Each institution will need to tailor the practice guidelines to fit the needs of the patients. Some cancer centers use protocols for research that have unpredictable capacity to produce CINV. This requires individualization of practice guidelines because of unknown emetogenic potential produced by the research protocols. For example, bone marrow transplantation may use doses and combinations of chemotherapy that may have profoundly higher emetogenic potential than what is seen in the literature. These regimens may require innovative treatment schemes to prevent CINV. The best approach to the transplantation population is to initiate treatment with combinations of dopamine-2 antagonists, serotonin antagonists, and corticosteroids in standard doses. Outcome data collection enables the pharmacotherapist to assess response and adjust therapy accordingly. Adjustment of dose and/or schedule of each agent may be necessary to

improve the outcome from a guideline schema. The major advantage of the use of guidelines is to provide an on-going methodology for the purpose of critical analysis. Prescribing patterns can be improved after appropriate data collection and assessment.

In summary, the formation of practice guidelines for CINV offers the clinician a tool for cost-effective use of antiemetics, which should improve the outcome of the patient at the lowest possible cost to the institution. Practice guidelines provide consistent rationale for treatment to provide a methodology for evaluation. By consistently applying practice guidelines, institutions can assess the effectiveness and make adjustments warranted to improve patient outcomes. The patient satisfaction and quality of life should be enhanced when CINV is controlled by evidence-based, practice guideline methodology, which is tested over time.

Figure 2

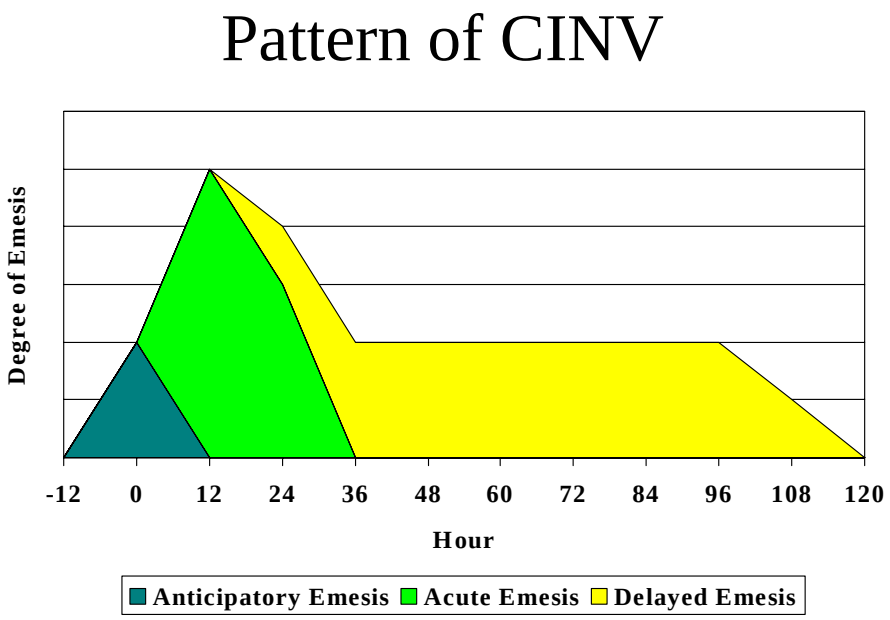

Pattern of CINV
Degree of Emesis
-12
0
12
24
36
48
60
72
84
96
108
120
Hour
Anticipatory Emesis
Acute Emesis
Delayed Emesis

Table 1

Relative Emetogenic Potential of Antineoplastic Agents

Level 5 VERY HIGH >90% Incidence	**Level 4** HIGH 60%-90% Incidence	**Level 3** MODERATE 30%-60% Incidence	**Level 2** LOW 10%-30% Incidence	**Level 1** VERY LOW <10% Incidence
Carmustine (>250 mg/m^2)	Busulfan (high dose)	Aldesleukin	Asparaginase	Bleomycin
Cisplatin (≥60 mg/m^2)...D	Carboplatin…D	Azacitidine	Cladribine	Busulfan (low dose)
Cyclophosphamide (1000 mg/m^2)	Carmustine (<250 mg/m^2)	Cyclophosphamide (<600 mg/m^2)...D	Docetaxel	Chlorambucil
Cytarabine (≥500 mg/m^2)	Cisplatin (<60 mg/m^2)...D	Cytarabine (<500 mg/m^2)	Etoposide	Hydroxyurea
Dacarbazine	Cyclophosphamide (≥600 mg/m^2)…D	Daunorubicin	Floxuridine	Interferon-α
Lomustine	Dactinomycin	Doxorubicin (≤40 mg/m^2)…D	Fludarabine	Mercaptopurine
Mechlorethamine	Doxorubicin (>60 mg/m^2)...D	Epirubicin	Fluorouracil	Tamoxifen
Pentostatin	Irinotecan	Idarubicin	Gemcitabine	Thioguanine
Streptozocin	Ifosfamide	Methotrexate (<1000 mg/m^2)	Melphalan (oral)	Vinblastine
	Methotrexate (≥1000 mg/m^2)	Mitomycin	Paclitaxel	Vincristine
	Mitoxantrone	Procarbazine	Teniposide	Vinorelbine
	Thiotepa (high dose)		Thiotepa (low dose)	
			Topotecan	

****Combination chemotherapy should be classified according to the highest emetogenic agent contained in the regimen.*****
****Agents followed by a "D" cause delayed emesis.*****

Table 2

Recommended Antiemetics and Adult Dosing for Prevention and Treatment of CINV[4,24]

ANTIEMETIC AGENT	DOSE RANGE	SCHEDULE	AWP PER DOSE
Serotonin Antagonists			
Dolasetron	IV: 1.8 mg/kg or 100 mg PO: 100 mg	Once, Prechemo	IV: $166.50 PO: $ 73.30
Granisetron	IV: 0.01 mg/kg or 1 mg PO: 2 mg	Once, Prechemo	IV: $195.20 PO: $ 94.10
Ondansetron	IV: 0.15 mg/kg or 8-24 mg PO: 12-24 mg	Once, Prechemo	IV: $ 48.90-$146.70 PO: $ 41.70-$ 83.40
Corticosteroid			
Dexamethasone	IV: 20 mg PO: 20 mg	Once, Prechemo	IV: $1.53 PO: $0.90
Dexamethasone	PO: 4-8 mg for delayed emesis	Two times daily for 2-3 days for delayed emesis	PO: $0.58/4 mg
Other Agents with Lower Therapeutic Index			
Metoclopramide	IV: 2 mg/kg	Once, Prechemo	$14.70/100 mg
Metoclopramide	PO: 20-40 mg for delayed emesis	Two to four times daily for 3-5 days for delayed emesis	$0.52/20 mg
Prochlorperazine	IV: 10-30 mg PO: 10-20 mg	Every 3-4 hours prn	IV: $4.70/10 mg PO: $0.89/10 mg
Haloperidol	IV: 1-4 mg PO: 1-4 mg	Every 6 hours prn	IV: $16.30/5 mg PO: $0.40/2 mg
Lorazepam	IV: 1 to 2 mg PO: 1 to 2 mg	Every 6 hours prn	IV: $0.92/1 mg PO: $0.88/1 mg
Dronabinol	PO: 5-20 mg	Every 3-6 hours prn	$6.63/5 mg

Table 3

Antiemetic Sites of Action and Major Side Effects[4]

Antiemetic Agents	Most Common Adverse Effects	Proposed Sites of Antiemetic Action
Antihistamine Diphenhydramine	Sedation, dry mouth, constipation, urinary retention	Histamine receptors
Benzamides Metoclopramide	Sedation, extrapyramidal effects, restlessness, diarrhea	Dopamine-2 receptors Serotonin receptors (high dose) Gastric emptying
Benzidiazepine Lorazepam	Sedation, amnesia, respiratory depression, ataxia, blurred vision, hallucinations	Cortex
Butyrophenones Droperidol Haloperidol	Sedation, hypotension, tachycardia, extrapyramidal effects	Dopamine-2 receptors
Cannabinoid Dronabinol	Sedation, euphoria, vasodilation, vision difficulties, confusion, dysphoria	Cortex
Corticosteroids Dexamethasone	Gastrointestinal upset, anxiety, insomnia, hyperglycemia	Unknown
Dopamine Antagonists Prochlorperazine Promethazine Chlorpromazine	Sedation, lethargy, skin sensitization, cardiovascular effects, extrapyramidal effects	Dopamine-2 receptors
Serotonin Antagonists Dolasetron Granisetron Ondansetron	Headache, asymptomatic prolongation of ECG interval	Serotonin receptors

Table 4

Antiemetic Therapy for Acute Chemotherapy-induced Nausea and Vomiting

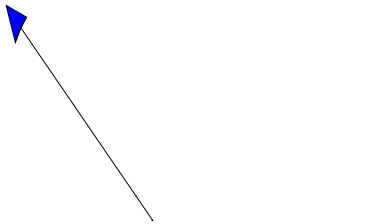
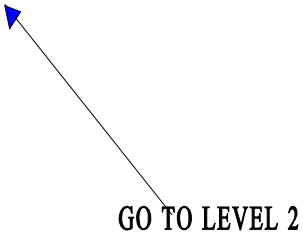
CHEMOTHERAPY EMETOGENIC LEVEL	FIRST-CHOICE THERAPY	TREATMENT FAILURES
5,4	***DEXAMETHASONE 20 mg IV/PO*** **+** ***SEROTONIN ANTAGONIST IV/PO***	***DEXAMETHASONE 20 mg IV/PO*** **+** ***METOCLOPRAMIDE OR DOPAMINE ANTAGONIST*** **+/-** ***DIPHENHYDRAMINE 25 mg***
3	***DEXAMETHASONE 20 mg IV/PO*** **+** ***SEROTONIN ANTAGONIST PO***	
2	***DEXAMETHASONE 20 mg IV/PO*** **+/-** ***PRN DOPAMINE ANTAGONIST***	

Table 5

Antiemetic Therapy for Delayed Nausea and Vomiting 24 Hours Postchemotherapy

	FIRST-CHOICE THERAPY	TREATMENT FAILURES
DELAYED NAUSEA AND VOMITING	**DEXAMETHASONE 8 mg PO BID X 3 DAYS + METOCLOPRAMIDE 20-40 mg PO QID X 3 DAYS**	**DEXAMETHASONE 8 mg PO BID X 3 DAYS + SEROTONIN ANTAGONIST PO/IV Dolasetron 100 mg PO Q day or Granisetron 2 mg PO Q day or Ondansetron 8 mg PO BID**

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