Optimal Use of Antiemetics in the Outpatient Setting

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Nausea and vomiting are the toxicities of chemotherapy most feared by the cancer patient. However, increased understanding of the mechanisms of nausea and vomiting has led to greatly improved control of this toxicity.

It is said that "necessity is the mother of invention." By the same token, advances in symptom management have become necessary due to the toxicities associated with advances in antitumor therapy. This is particularly true in the area of antiemetics. As chemotherapeutic agents of greater therapeutic and emetogenic potential came into common use, it became necessary to improve our understanding of the mechanisms of chemotherapy-induced emesis and to develop more potent and more effective antiemetics.

In recent years, the administration of chemotherapy has rapidly changed from a highly technical hospital-based procedure to a routine outpatient procedure. However, every advance has a price. On the one hand, more effective supportive care agents eliminated the necessity for intensive in-hospital care for the patient receiving chemotherapy. On the other hand, this change in the venue of chemotherapy administration now requires a capacity for effective administration of these protective agents in the outpatient setting as well. Fortunately in the case of antiemetics, this transition has been relatively unremarkable. Improved understanding of the dose-response characteristics of antiemetics and the time course of various types of emesis led to the realization that antiemetic management is virtually identical in the outpatient and inpatient settings. The one caveat is that health-care professionals need to be more vigilant in the outpatient setting, because much of the potential emetic response will occur at home, away from the medical facility.

As patient preferences and concerns regarding quality-of-life issues have been taken into greater consideration, the importance of effective antiemetic control has been further appreciated. In a survey of patient concerns published in 1983,[1] nausea and vomiting were found to be the two toxicities of chemotherapy most feared by patients. One could object that this survey was conducted well before the era of modern antiemetics and, therefore, this ranking might be attributed to ineffective antiemetic control. However, when the survey was repeated a decade later,[2] nausea was still ranked the first and vomiting the fifth most significant side effect of chemotherapy.

Mechanisms of Emesis

To devise effective strategies for the prevention of chemotherapy-induced emesis, one must first understand the causes and mechanisms of emesis. It is particularly important to remember that vomiting is a physiologic rather than a pathologic process. Vomiting is the body’s natural defense against the ingestion of toxic substances and is the most effective method to rid oneself of such toxins. Vomiting only appears pathologic in the clinical setting because many oncologic emetogenic agents are administered parenterally, while the body’s defenses remain the same.

Emetic Reflex Arc

Since emesis is a basic defensive mechanism, it is not surprising to find that this response is controlled by a basic reflex arc.[3] The emetic reflex arc is a multiafferent system with potential stimulation through neuroreceptors located in the chemoreceptor trigger zone in the brain stem, the upper gastrointestinal tract wall (peripheral pathway), the cerebral cortex (learned or anticipatory vomiting), and the vestibular organs (motion sickness).

The emetic response is coordinated through the emetic center located in the brain stem in the region of the nucleus tractus solitarius. Efferent neural impulses are then transmitted to the multiple effector organs of the gastrointestinal, respiratory, and musculoskeletal systems that must be coordinated for an effective emetic response. This transmission of neural impulses passes through numerous synapses between the initial stimulatory event and the ultimate emetic response. Identification and blockade of relevant neurotransmitters and neurotransmitter receptors within the
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The emetic reflex arc has proven to be the cornerstone of antiemetic therapy. As the list of potentially relevant neurotransmitters has expanded,[4] the flexibility and effectiveness of antiemetic therapy has expanded as well.

Early Antiemetic Agents

The first formal clinical trials of antiemetics were performed in the 1960s and concentrated on dopamine (D2)-receptor antagonists.[5] The phenothiazines and the butyrophenones were shown to be effective antiemetics against chemotherapy-induced emesis and became the mainstays of antiemetic therapy. However, such therapies became inadequate as new chemotherapeutic agents with greater emetogenic potential were developed. Against a highly emetogenic agent such as cisplatin, which was introduced in the mid-1970s, traditional standard-dose antiemetics were little better than placebo.[6] This situation changed with the publication of a single clinical trial.

Metoclopramide

One agent had been of particular interest to researchers in the antiemetic field. Metoclopramide, which was used for the treatment of gastroparesis and for the performance of radiologic procedures, was known to be a D2 antagonist and a prokinetic agent, both properties that should theoretically be valuable in the prevention of chemotherapy-induced emesis. However metoclopramide at standard doses was as ineffective as other agents of the time against cisplatin-induced emesis.

In 1981, Gralla et al.[6] took advantage of the concept of dose-response, commonly used as a basis for dose escalation in phase I studies of cytotoxic agents, and applied this concept to the field of supportive care. When the dose of metoclopramide was escalated 25-fold, the number of acute vomiting episodes after administration of cisplatin decreased by over 90% (from a median of 11 to a median of 1). Addition of a corticosteroid increased the antiemetic efficacy even further.[7]

5-HT3-Receptor Antagonists

The next major advance in antiemetic therapy resulted from the identification of another important neurotransmitter receptor. Antidopaminergic toxicity (akathisia, oculogyric crisis, anxiety, depression) had become a significant problem in the administration of high-dose metoclopramide. However, unlike standard-dose metoclopramide, which effectively blocked only the D2 receptor, high-dose metoclopramide blocked both the D2 receptor and the serotonin (5-HT3) receptor.[8] Since the 5-HT3 receptor also appeared to have a role in the induction of emesis, the separation of antiemetic efficacy from antidopaminergic toxicity through the use of specific 5-HT3 antagonists became theoretically possible.

Ondansetron (Zofran) was the first 5-HT3 antagonist studied and introduced into clinical practice in the United States. In early dose-ranging studies,[9,10] this agent was found to have activity equivalent to that of high-dose metoclopramide over a wide range of doses, with an extremely mild toxicity profile. Granisetron (Kytril)[11] and dolasetron (Anzemet)[12] were later found to have similar properties. As with the earlier antiemetic families, the addition of a corticosteroid markedly enhanced the antiemetic efficacy of the 5-HT3 antagonists.[13]

Cost-effective, efficient outpatient use of the 5-HT3 antagonists for prevention of acute chemotherapy-induced emesis was originally hampered by inconvenient dosing schedules and high cost. Further steps in development therefore concentrated on questions of schedule, route, and dose.

Dosing Schedule

Ondansetron, granisetron, and dolasetron all have serum half-lives ranging from 4 to 10 hours.[14] Ondansetron, with the shortest half-life, was originally administered in three divided doses over 8 hours in the belief that such a schedule would be necessary to sustain antiemetic protection.[9,10] Such a schedule would have been impractical for use in a busy outpatient setting. However the extended schedule also proved to be unnecessary.

In 1990, Marty and colleagues[15] treated 305 patients receiving cisplatin with ondansetron, 32 mg, given intravenously either as a single bolus or as an 8-mg loading dose followed by a 1-mg/h continuous infusion for 24 hours. Prevention of nausea and vomiting was identical in both groups, suggesting that treatment with a single dose during the initial hours after chemotherapy was sufficient for 24-hour protection despite the short half-life.

Route of Administration

Although the intravenous route is the route most commonly used, attempts have also been made to deliver antiemetics by the respiratory, transdermal, buccal, rectal, nasal, and oral routes. Greatest attention has been focused on oral administration because of its convenience, patient satisfaction.
with self-administration, and cost savings due to the minimal pharmacy preparation and nursing administration time involved. That said, the oral route would not have gained general acceptance if a decrement in antiemetic efficacy had been noted.

In two studies, each with more than 1,000 patients, Gralla et al[16] (Table 1) and Perez et al[17] (Table 2) compared oral granisetron to intravenous ondansetron in patients receiving the highly emetogenic agent cisplatin or moderately emetogenic chemotherapy, respectively. Patients could receive corticosteroids at investigator discretion, and approximately two-thirds of the patients did receive this additional therapy. Efficacy was identical between the two regimens in both the overall groups and the large subsets receiving corticosteroids as well.

Spector et al[18] reversed the antiemetic agents, comparing intravenous granisetron to oral ondansetron in the treatment of patients receiving cisplatin, and achieved similar results. Thus, the oral route has equivalent efficacy to the intravenous route for 5-HT3 antagonists that are administered at appropriate doses.

### Antiemetic Dose

The best dose of a drug is the lowest dose that is fully effective, as this will be the most cost-effective strategy and the strategy most likely to avoid unnecessary dose-related side effects. However, identification of the lowest fully effective dose is not always straightforward. The fact that approved doses of various 5-HT3 antagonists differ between countries, with the approved dose of ondansetron being higher and the approved dose of granisetron being lower in the United States than in Europe, suggests significant flexibility in dosing.

In 1994, Hesketh et al[19] classified chemotherapeutic regimens as having high, moderate-high, or moderate emetogenicity and treated patients receiving these regimens with ondansetron at 32, 24, or 8 mg, respectively (all in combination with dexamethasone, 20 mg). No loss of antiemetic effectiveness was noted, providing documentation that dose de-escalation under certain circumstances is feasible. Nevertheless, because the dose of ondansetron varied with the emetogenicity of the regimen, the question of whether the standard dose of ondansetron (32 mg for patients receiving cisplatin) was appropriate or whether efficacy within a category might be compromised by dose de-escalation was not addressed.

DiPiro et al[20] examined this question in patients receiving moderately emetogenic chemotherapy, randomizing patients to receive ondansetron at either 32 or 20 mg (both with dexamethasone, 10 mg). No loss of efficacy attributable to ondansetron dose de-escalation was noted. Pectasides et al[21] looked at the same question in patients receiving highly emetogenic (cisplatin) chemotherapy. Patients were randomized to receive ondansetron, 24 or 8 mg (both with dexamethasone 20 mg), and equivalent antiemetic protection was still seen in both groups.

Of note, ondansetron dose de-escalation in the Pectasides study[21] was greater than that in the DiPiro study[20] despite the greater emetogenicity of the challenge agent. This variation in fully effective doses can be understood through review of the dose-response curves of the 5-HT3 antagonists (Figure 1). When data from dose-ranging studies of ondansetron, granisetron, or dolasetron are plotted, a logarithmic rather than linear dose-response curve is seen.[22] All of these curves have a steep slope at lower doses followed by a therapeutic plateau once a threshold dose value has been surpassed. Although the numeric doses of the various agents may differ, the level of complete antiemetic protection at the plateau doses is the same.

Thus, dose de-escalation is possible as long as the dose remains above the threshold value for that agent. By the same token, dose escalation beyond a dose that surpasses the threshold value will not result in a significant increase in efficacy (although some increase in toxicities such as headache and constipation may be seen).

The threshold values for the commonly used 5-HT3 antagonists, when used against the "gold standard" highly emetogenic agent cisplatin, are still not fully defined. Definition of the threshold value for 5-HT3 antagonists used against moderately emetogenic chemotherapy (for which the threshold value will be lower) or against bone marrow transplant regimens (for which the threshold value may be higher) present future challenges.[23]

### Potency and Specificity

While it is valuable to recognize the marked similarities between the 5-HT3 antagonists, it is also valuable to recognize the potential differences. Potency and specificity are two areas that have been considered in this regard. Although potency may define full dose and reflect receptor-binding affinity, no clinically significant difference in level of efficacy has been noted between agents used at or above their threshold efficacy dose values.[22] In contrast, differences in binding specificity have certainly been described.[24] In addition to marked affinity for the 5-HT3 receptor, compounds related to dolasetron may also have measurable binding affinity for the 5-HT2 receptor, whereas...
ondansetron has measurable binding affinity for the 5-HT1B, 5-HT1C, and opiate mu receptors (Table 3). Theoretically, binding specificity (or lack of specificity) should not be as important as the function of the secondary receptor. If the secondary receptor adds additional antiemetic efficacy, then the lack of specificity is advantageous. If the secondary receptor adds only additional toxicity, then the lack of specificity is disadvantageous. Practically, secondary neuroreceptor binding has not yet been shown to provide additional clinically significant efficacy or toxicity for any of the currently available 5-HT3 antagonists.

If effective antiemetics are not used, the most frequent and severe episodes of emesis will occur during the first 24 hours after administration of chemotherapy. Success in the management of this acute vomiting has allowed increased attention to be focused on other forms of vomiting. Anticipatory emesis (ie, vomiting before the administration of chemotherapy) is a learned response conditioned in large part by the occurrence of emesis after prior chemotherapy.[25] Elimination of the conditioning emetic event through the aggressive use of currently available antiemetics is the most important prevention strategy.

Control of delayed emesis (ie, vomiting that begins more than 24 hours after the administration of chemotherapy) has proven to be more difficult. The prevalence of this problem was only recognized from patient surveys demonstrating that, despite excellent control of acute emesis, over 70% of patients receiving cisplatin have some nausea or vomiting within the next 4 days.[26] Different mechanisms for acute and delayed vomiting were suggested by the lack of efficacy of standard acute antiemetic agents against delayed vomiting.

Dexamethasone is probably the most effective single agent against delayed emesis, decreasing the incidence of such events by approximately 20%.[27] Metoclopramide[27] or 5-HT3 antagonists[28] may decrease this incidence by an additional 10%. However, these efficacy results are markedly inferior to those expected from the level of efficacy of these agents in the setting of acute vomiting.

**NK-1-Receptor Antagonists**

A breakthrough in the understanding and treatment of delayed emesis came with the identification of an additional relevant neurotransmitter and neurotransmitter receptor. A member of the neurokinin (NK) receptor family, the NK-1 receptor is the site of binding by substance P. Although the NK-1 receptor is generally associated clinically with pain perception, this receptor also has a role in pathways that regulate inflammation, salivation, vasodilatation, depression, plasma protein extravasation, and emesis.[29]

In preclinical studies, NK-1 receptor antagonists demonstrated protective activity against emesis induced by a wide range of stimuli, including cisplatin, copper sulfate, morphine, nicotine, apomorphine, ipecac, cyclophosphamide (Cytoxan, Neosar), and radiation.[30] Several NK-1 antagonists have now entered clinical trials.

In a single-agent study, Cocquyt et al[31] randomized patients receiving cisplatin to antiemetic treatment with the NK-1 antagonist prodrug L-758298 or ondansetron. Although complete protection from acute vomiting was more common with ondansetron (52% vs 37% of patients), complete protection from delayed vomiting was markedly more common with the NK-1 antagonist (72% vs 30% of patients). Most recent studies have therefore combined an NK-1 antagonist with a standard 5-HT3 antagonist and dexamethasone to attempt to prevent both acute and delayed emesis.

In a randomized double-blind investigation of patients receiving cisplatin, Navari et al[32] administered a standard granisetron/dexamethasone regimen with either (1) an NK-1 antagonist (L-754030) for 5 days, (2) the NK-1 antagonist on the day of treatment followed by placebo for 4 days, or (3) placebo for 5 days. Addition of the NK-1 antagonist resulted in a moderate increase in the prevention of acute emesis and a marked increase in the prevention of delayed emesis, confirming the preclinical and earlier clinical results (Table 4).

Chawla et al[33] recently presented the results of a dose-ranging study of ondansetron, dexamethasone, and the NK-1 antagonist MK-869, in which dexamethasone was continued for several days as well. A further improvement in overall control of delayed emesis was suggested, although this observation must now be confirmed in a randomized double-blind phase III trial.

**Future Directions**

Because advances in antiemetic therapy have historically depended on the identification of new relevant neurotransmitter receptors, it is only reasonable to speculate that further advances will continue to come from this source. Candidate neurotransmitter receptors can be found within the
Opiates
The opiates have had a particularly complex history. Administration of increasing doses of loperamide or morphine to the ferret will result in increasing emesis at lower doses, but a further increase in dose will cause suppression of the emetic response.[34] Fentanyl is not emetogenic but will prevent emesis attributed to a number of sources, including morphine challenge.[35] Naloxone will reverse fentanyl protection from emesis.[35] However, in a clinical setting, naloxone administered in the absence of opiates will itself increase chemotherapy-induced emesis.[36] This seemingly contradictory pattern can be explained by postulating a role for endogenous opioids in protection from emesis and by the existence of numerous opiate receptor subtypes, some of which may be emetogenic and some of which may be antiemetic in function.[37,38] Development of modulators that are specific for certain promising opiate receptor subtypes (such as the mu-1 receptor) may result in a new family of antiemetics and may allow separation of opiate efficacy and toxicity.

Cannabinoids
The cannabinoids are another intriguing and promising family of compounds for potential drug development. The antiemetic efficacy of these agents was first demonstrated by Sallan et al,[39] who noted a response to delta-9-THC in 14 of 17 young chemotherapy patients refractory to standard antiemetics. Although there is a cannabinoid currently available for treatment of refractory emesis, a moderate-to-severe toxicity profile has contributed to the lack of common use of this agent.[40] However, recent descriptions of the function of various cannabinoid receptor subtypes raise the possibility of more specific agents with better efficacy/toxicity ratios. The CB1 receptor, for example, is associated with orexigenic/anorexigenic pathways (qualitatively similar to nausea pathways).[41] The CB1 receptor can also modulate dopaminergic pathways, providing a link to previous antiemetic agents.[42] As nonpsychoactive cannabinoid derivatives with analgesic and anti-inflammatory properties have already been described,[43] it is possible that oral nonpsychoactive cannabinoid derivatives with antiemetic properties can also be developed, thereby avoiding the most troublesome toxicities of these agents.

Conclusions
In conclusion, effective outpatient antiemetic management depends on the availability of effective antiemetic agents, appropriate use of such agents, and an understanding of the various types of emesis and levels of emetogenicity and the appropriate therapeutic interventions for each. Several different families of effective antiemetic agents are commercially available, and our knowledge of types of emesis and levels of emetogenicity can be used to guide their use. Further progress will depend on the identification of additional neurotransmitter receptor targets. Several promising leads in this area are under investigation.

References:


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