Best Practice Management of CINV in Oncology Patients: I. Physiology and Treatment of CINV

Multiple Neurotransmitters and Receptors and the Need for Combination Therapeutic Approaches

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The etiology of nausea and vomiting is multifactorial, and the relevant pathways often involve multiple neurotransmitters and receptors. Thus, optimal pharmacologic therapy that modulates several neurotransmitter and receptor systems will likely be necessary to prevent chemotherapy-induced nausea and vomiting (CINV).

It is believed that CINV occurs largely via (1) a peripheral pathway involving activation of neurotransmitters as a result of local gastrointestinal (GI) irritation or damage and (2) a central pathway involving activation of neurotransmitters in the chemoreceptor trigger zone (CTZ) directly through the blood or cerebrospinal fluid. The currently accepted model includes these two pathways and the neurotransmitters that are critical in the development of CINV. The peripheral pathway is activated by serotonin (5-hydroxytryptamine, 5-HT) that is released by damaged or otherwise activated enterochromaffin cells (which contain approximately 80% of the body’s supply of serotonin) and induce emesis by binding to serotonin type 3 (5-HT3) receptors along the vagus nerve in the GI tract. Afferent vagal nerve impulses are thought to be transmitted to the CTZ and vomiting center of the brain. The central pathway is activated by substance P, which is abundant in the CTZ of the area postrema and is present in small amounts about GI vagal efferent nerve fibers. Substance P induces vomiting by binding to neurokinin-1 (NK1) receptors, which are highly concentrated in the brain. However, in addition to serotonin and 5-HT3 receptors, and substance P and NK1 receptors, other neurotransmitter and receptor systems may play important roles in the vomiting response. These include serotonin and 5-HT4 receptors; dopamine (D) and D1 and D2 receptors; cannabinoids (CBs) and CB1 receptors; histamine (H) and H1 receptors; acetylcholine and the muscarinic (M) acetylcholine M3 and M5 receptors; and γ-aminobutyric acid (GABA) and GABAβ receptors. In fact, more than two dozen neurotransmitter and receptor systems have roles in the vomiting reflex; however, the relationships among them have not been completely elucidated, and pharmacologic agents for modulating their activity may as yet be unavailable. The known sites of action of available classes and agents for managing CINV, to elucidate the roles of additional neurotransmitters and receptors in both nausea and vomiting, and to develop new antiemetic agents.

Abstract

Chemotherapy-induced nausea and vomiting (CINV) involves multiple neurotransmitter and receptor systems; thus, its optimal treatment is likely to require a combination of therapies targeting multiple systems. Antiemetic regimens have evolved from use of dopamine antagonists alone to combination regimens such as a corticosteroid plus an antagonist of the serotonin (5-hydroxytryptamine) type 3 receptor or this combination with a neurokinin-1 receptor antagonist. The net result is that antiemetic efficacy has markedly increased with the addition of each new class of agent to treatment regimens. Further research is needed to determine optimal uses of available classes and agents for managing CINV, to elucidate the roles of additional neurotransmitters and receptors in both nausea and vomiting, and to develop new antiemetic agents.

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CINV highlights several major advances after the use of phenothiazines, such as prochlorperazine, alone. \(^3\) Subsequently, corticosteroids were shown to be superior to placebo in treating CINV in the late 1970s, and, by the early 1980s, high-dose metoclopramide was shown to be more effective than phenothiazines. In addition, antiemetic control was superior when high-dose metoclopramide and a corticosteroid such as dexamethasone were administered together.

Similarly, clinical trials in the late 1980s and early 1990s demonstrated superior efficacy of 5-HT\(_3\) receptor antagonists over older antiemetics to control CINV from highly emetogenic chemotherapy (HEC). \(^4\) The activity of 5-HT\(_3\) antagonists was also enhanced by the addition of a corticosteroid.

Clincial research from then to now has also confirmed that the addition of D\(_2\) receptor antagonist to a 5-HT\(_3\) receptor antagonist regimen may improve antiemetic control, that a corticosteroid plus a 5-HT\(_3\) receptor antagonist also improves control of CINV from moderately emetogenic chemotherapy (MEC), and that NK\(_1\) receptor antagonists also add efficacy when combined with a 5-HT\(_3\) antagonist and a corticosteroid for both HEC and MEC.

### Characteristics and Use of Current Antiemetic Regimens

#### USE OF DEXAMETHASONE WITH 5-HT\(_3\), RECEPTOR ANTAGONISTS

In the author’s experience, dexamethasone is far too frequently not included as an essential agent in a combination antiemetic regimen with a 5-HT\(_3\) antagonist. This is an important point, particularly because a large meta-analysis of studies that compared the combination with a 5-HT\(_3\) antagonist alone clearly showed the combination is superior for preventing acute emesis. \(^5\) The addition of dexamethasone improves control of emesis by 15%–20% and should be given with a 5-HT\(_3\) antagonist unless contraindicated or not tolerated.

#### METOCLOPRAMIDE IN DELAYED EMESIS

De Mulder and colleagues\(^6\) conducted a study to compare the first-generation 5-HT\(_3\) receptor antagonist ondansetron with metoclopramide, which is a strong dopamine receptor antagonist and a weak 5-HT\(_3\) receptor antagonist. In the study, 79 patients receiving cisplatin (50–100 mg/m\(^2\)) were treated with ondansetron (8 mg IV followed by 1 mg/h on day 1 and 8 mg orally three times per day on days 2–6) or metoclopramide (3 mg/kg IV followed by continuous infusion on day 1 and 20 mg orally three times per day on days 2–6). Patients who received ondansetron were more likely to have no vomiting episodes on day 1 (72% vs 41%), whereas the rates of no emesis were similar on days 2–5 for the ondansetron and metoclopramide groups (63% vs 62%). It is important to remember that high doses of metoclopramide are also more likely to cause extrapyramidal symptoms, which are associated with dopamine antagonists, so patients in this study also received diphenhydramine.

In addition, inadequately controlled acute CINV is a primary risk factor for delayed CINV, so the fact that metoclopramide was much less likely to control acute vomiting but equivalent to

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**Figure 1** Sites of Action of Different Classes of Antiemetic Agents

CB = cannabinoind; D = dopamine; NK = neurokinin; S-HT = 5-hydroxytryptamine (serotonin)

Adapted from Hornby\(^2\)

It has proven even more difficult to identify neurotransmitter and receptor systems and interrelationships involved in nausea. Moreover, nausea is often problematic even when emesis is controlled. This further supports the notion that numerous neurotransmitter and receptor systems are involved in CIN and CINV, underscoring the need for treatments that target multiple systems.

### Classification of CINV

CINV commonly is classified as acute—occurring and resolving within 24 hours of chemotherapy; delayed—occurring at > 24 hours after chemotherapy administration; breakthrough—occurring despite antiemetic treatment; refractory—unmanageable with current antiemetics; and anticipatory—a conditioned response after prior, inadequately controlled CINV. Anticipatory nausea is most common.

It bears noting that although both overlapping and differing mechanisms clearly are involved in acute as well as delayed CINV, the 24-hour criterion was established based on the emetic activity after cisplatin administration and to evaluate responses in antiemetic trials with that agent. Hence, this model does not explain the underlying physiology of CINV from all chemotherapy agents, and the 24-hour mark is not a magic number that neatly delineates acute and delayed physiologic responses.

It should also be noted that anticipatory CINV may not solely be a conditioned response to prior inadequately prevented CINV. That is, patients may have experienced nausea or vomiting from other causes before their first chemotherapy, or they may expect to experience these adverse effects after chemotherapy based on information they hear or read. This component of anticipatory CINV should be taken into account in efforts to manage these adverse effects of treatment.

### Development of Antiemetic Therapies

A timeline of development of antiemetic treatments for
ondansetron for controlling delayed CINV suggests that the dopamine-antagonist effect of metoclopramide is important for preventing delayed symptoms. Furthermore, it is not possible to rule out some modest diphenhydramine-induced antiemetic effect.

DIFFERENCES AMONG 5-HT3 RECEPTOR ANTAGONISTS

Although response rates in individual trials comparing first-generation 5-HT3 receptor antagonists sometimes differed, overall efficacy of these agents is similar in the settings of HEC and MEC.3 Palonosetron is a second-generation 5-HT3 receptor antagonist with a half-life of approximately 40 hours (compared with 4–8 hours for first-generation agents; Table 1).8,9 Two parallel trials of 1,132 patients receiving MEC compared single IV doses of palonosetron, 0.25 mg or 0.75 mg, with single IV doses of ondansetron, 32 mg, in a first trial10 or dolasetron, 100 mg, in the second trial.11 Corticosteroids were administered to only approximately 5% of patients in these trials. Pooled results showed significantly higher rates of complete control of emesis with palonosetron 0.25 mg (n = 378) versus ondansetron or dolasetron (n = 376) in the acute time frame (72.0% vs 60.6%), the delayed time frame (60.0% vs 46.8%), and overall (57.7% vs 42.0%; all P < 0.025).12 Results of the trial comparing palonosetron with ondansetron are shown in Figure 2.12 There was no significant difference in treatment failure rates between palonosetron and ondansetron, but the separation of the curves for the palonosetron groups versus the ondansetron group after 24 hours indicates that palonosetron’s longer half-life was associated with some preventive benefit as no further therapy was given past day 1 in the ondansetron and dolasetron arms. This observation, in turn, indicates that serotonin does indeed play a role in delayed emesis. The results of these studies also serve as a reminder that without combination therapy, treatment with 5-HT3 inhibitors, whether they are long-acting or not, will still fail in some 40%–50% of patients. This also highlights that serotonin receptor antagonists should not generally be used alone for preventing delayed CINV.

CYP2D6 ULTRARAPID METABOLISM

Cytochrome P450 (CYP) enzymes metabolize 5-HT3 receptor antagonists (Table 1).8,9 CYP2D6 is responsible for the majority of metabolism of dolasetron and palonosetron and partially for metabolism of ondansetron, whereas CYP3A4 is responsible for the majority of metabolism of granisetron and partially for metabolism of ondansetron. It has been shown that genetic polymorphisms in CYP2D6 can dramatically alter the antiemetic effects of agents metabolized by that enzyme. Individuals can be categorized as poor metabolizers (having two deficient alleles), intermediate metabolizers, extensive metabolizers (comprising the majority of the population), or ultrarapid metabolizers (having duplicated or amplified active alleles) who clear drug so rapidly it appears to decrease the therapeutic effect of agents having a short half-life.3,13 As shown in Figure 3,13 patients receiving chemotherapy who have three active 2D6 genes (ie, are ultrarapid metabolizers) have a significantly greater mean number of acute and delayed emesis episodes when given ondansetron or tropisetron (also metabolized by 2D6). The data also suggest that ultrarapid metabolism was associated with increased severity of nausea. Interestingly, it appears that metabolism has a smaller effect on palonosetron, as pharmacokinetics for this agent vary only slightly between poor and extensive metabolizers.15

TRANSDERMAL GRANISETRON

A transdermal formulation of granisetron has been developed in the attempt to prolong drug activity. In a recent randomized, double-blind, phase III noninferiority trial, 582 patients receiving multiday HEC or MEC were given pills (placebo or active drug) for 3–5 days and an opposite transdermal patch (active drug or placebo) for 6 days starting 1 day before chemotherapy.16 The oral granisetron dosage was 2 mg per day, and the total patch dose was 34.3 mg with an average daily absorption of 3.1 mg. There was no significant difference in complete response rates between patients receiving the patch and those receiving oral granisetron (60% vs 64%). The patch option is particularly attractive in the setting of multiday chemotherapy or radiation therapy regimens, and in facilitating antiemetic treatment in patients in whom CINV might make oral administration difficult.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pharmacologic Differences Among Serotonin (5-Hydroxytryptamine) Type 3 (5-HT3) Receptor Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGENT</td>
<td>pKi (log[Ki])</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>10.45 ± 0.2</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8.39 ± 0.1</td>
</tr>
<tr>
<td>Granisetron</td>
<td>8.91 ± 0.03</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>7.6</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450, Ki = dissociation constant, T1/2 = half-life

Source: “Wong et al” and “Clark et al”

Figure 2  Time to Treatment Failure with Palonosetron vs Ondansetron

Treatment failure was defined as a first emetic episode or use of rescue medication. Patients received single IV doses of palonosetron, 0.25 or 0.75 mg, or ondansetron, 32 mg, in the setting of moderately emetogenic chemotherapy. From Gralla et al.10
The success of a combination therapy approach to CINV is again emphasized by outcomes with addition of the NK₁ antagonist aprepitant to 5-HT₃ receptor antagonist and corticosteroid treatment. Hesketh and colleagues⁰ and Poli-Bigelli and colleagues¹ completed two phase III trials of patients receiving cisplatin-based chemotherapy, which showed 20% improvements in complete response rates (73% vs 52% and 63% vs 43%, respectively) with the addition of aprepitant to standard ondansetron plus dexamethasone. A notable finding in these studies was the larger benefit for women compared with men. For instance, in phase III trials of aprepitant plus ondansetron and dexamethasone versus ondansetron and dexamethasone alone (control group), the rate of complete response of acute emesis was 86% in women receiving aprepitant and 66% in the control group (P < 0.001).¹⁹ The benefit of adding aprepitant conferred a significant, but smaller, difference in control of acute emesis in men (response rates of 87% vs 80%, P < 0.05).

Another recent phase III trial compared aprepitant (125 mg on day 1 and 80 mg on days 2 and 3) plus ondansetron (8 mg twice daily on day 1) and dexamethasone (12 mg on day 1) with a regimen of ondansetron (8 mg twice daily on days 1–3) plus dexamethasone (20 mg on day 1) in women with breast cancer receiving MEC.¹² The addition of aprepitant significantly increased the 5-day complete response rate from 43.5% to 51.0% (P < 0.05) and the 5-day no-emesis rate from 59.0% to 76.0% (P < 0.001). Again, the gender disparity suggests that NK₁ plays an especially important role in CINV in female patients, which may help change the fact that women have consistently exhibited antiemetic treatment response rates 10%–20% lower than those men in antiemetic trials of both HEC and MEC done before the advent of NK₁ antagonists.¹,²¹

Some evidence indicates that the first 125-mg dose of aprepitant results in blockade of approximately 80% of NK₁ receptors in the brain.²² Although aprepitant is currently approved as a 3-day regimen, ongoing studies are attempting to determine whether additional doses contribute significantly to the efficacy of this agent, and for what period of time. A recent small study compared 1 day versus 3 days of aprepitant, both in combination with palonosetron on day 1 and dexamethasone on days 1–4.¹³ Interestingly, there were no differences in outcome for emesis, nausea, or use of breakthrough medications between the two arms.

It should be remembered that aprepitant is a moderate CYP3A4 inhibitor, with effects in this regard similar to those of grapefruit juice, diltiazem, and verapamil. Thus, it is recommended that dexamethasone, which is metabolized by CYP3A4, be used at a reduced dose when combined with aprepitant. Additionally, there may be a potential drug interaction between aprepitant and chemotherapeutic agents such as ifosfamide that also are metabolized by CYP3A4. A recent retrospective review involving 45 patients who received ifosfamide with or without aprepitant found that 6 of 8 patients experiencing ifosfamide neurotoxicity were also receiving aprepitant.²⁴ In the author’s experience, an option for patients receiving ifosfamide would be to give aprepitant starting the day after the final dose of ifosfamide, because delayed nausea and delayed vomiting are major problems with this chemotherapeutic agent. Thus, giving aprepitant at the end of ifosfamide dosing can avoid a potential drug interaction while providing coverage for delayed symptoms.

OLANZAPINE

Olanzapine is a US Food and Drug Administration–approved antipsychotic that blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine.²³ Many of these transmitters are involved in CINV. Olanzapine is a US Food and Drug Administration–approved antipsychotic that blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine.²³ Many of these transmitters are involved in CINV, and olanzapine has been shown to be effective in prevention of these adverse effects. A phase II trial evaluated the efficacy of olanzapine added to granisetron plus dexamethasone on day 1 and added to dexamethasone in the delayed period.²⁶ Results showed a very high rate of complete response and excellent con-
trol of nausea. A second phase II study combined palonosetron with dexamethasone plus olanzapine; the dexamethasone was given on day 1 only, and the olanzapine was given on days 2–4 after chemotherapy administration.27 For the first cycle of chemotherapy, the complete response rate was 100% in the acute period and 75% in the delayed period. Further studies are needed to define the comparative efficacy of olanzapine; however, it does appear to be an active agent in the prevention of CINV.

**Conclusion**

A thorough understanding of the pathophysiology of CINV is essential for its treatment. Realizing that there are multiple neurotumors involved leads to the design of appropriate antemetic combinations. Because CINV results from activation of numerous emetic pathways, including serotonin, substance P, and dopamine pathways, combination pharmacologic therapy is required to prevent acute and delayed symptoms. All of the current nationally recognized guidelines for prevention of CINV recommend combination therapy approaches, and it is imperative that these principles are understood and followed to provide the best outcome and quality of life for patients with cancer.

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