Treatment of chemotherapy-induced nausea

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The purpose of this review is to evaluate the effectiveness of the various antiemetic agents currently in use for the prevention of chemotherapy-induced nausea and to provide suggestions for the prevention of chemotherapy-induced nausea. The current data in the literature from numerous large studies suggest that the first- or second-generation 5-hydroxytryptamine-3 (5-HT_3) receptor (serotonin) antagonists and the neurokinin-1 (NK-1) receptor (substance P) antagonist aprepitant have not been effective in the control of nausea in patients who receive either moderately or highly emetogenic chemotherapy, despite the marked improvement in the control of emesis with these agents. Recent phase II and III studies with olanzapine have demonstrated good control of emesis and nausea in patients receiving either moderately or highly emetogenic chemotherapy. Preliminary small studies with gabapentin, cannabinoids, and ginger are inconclusive in defining the role of those three agents, if any, in the prevention of chemotherapy-induced nausea and vomiting.

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment.[1] The use of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists plus dexamethasone has significantly improved the control of CINV.[2] Recent studies have demonstrated additional improvement in the control of CINV with the use of three new agents: palonosetron (Aloxi), a second-generation 5-HT_3 receptor antagonist[3]; aprepitant (Emend), the first agent available in the drug class of neurokinin-1 (NK-1) receptor antagonists[4,5]; and olanzapine (Zyprexa), an antipsychotic that blocks multiple neurotransmitters in the central nervous system.[6–8]

The primary endpoint used for studies evaluating various agents for the control of CINV has been complete response (CR; no emesis, no use of rescue medication) over the acute (24 hours after chemotherapy), delayed (24-120 hours), and overall (0-120 hours) periods.[2] Recent studies have shown that the combination of a 5-HT_3 receptor antagonist, dexamethasone, and an NK-1 receptor antagonist have been effective in controlling emesis in patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) over a 120-hour period following chemotherapy administration.[4,5] Many of those studies have measured nausea as a secondary endpoint and have demonstrated that nausea has not been well controlled.[2–5]

Emesis is a well-defined event that is easily measured, but nausea may be more subjective and more difficult to measure. There are, however, two well-defined measures of nausea that seem to be effective, reproducible measurement tools: the Visual Analogue Scale (VAS) and the Likert scale.[9] The VAS is a scale from 0 to 10 or 0 to 100, with 0 representing no nausea and 10 or 100 representing maximal nausea. The Likert scale offers respondents the options of rating their nausea as none, mild, moderate, or severe.

Definition and pathophysiology

Nausea is a subjective, difficult-to-describe, sick or queasy sensation (usually perceived as being in the stomach) that is sometimes followed by emesis.[9] Nausea and emesis are not necessarily on a continuum. One can experience nausea without emesis, or one can have sudden emesis without nausea. It has been assumed that nausea is the conscious awareness of unusual sensations in the "vomiting center" of the brain stem (Figure 1), but the existence of such a center and its relationship to nausea remain controversial.[9]

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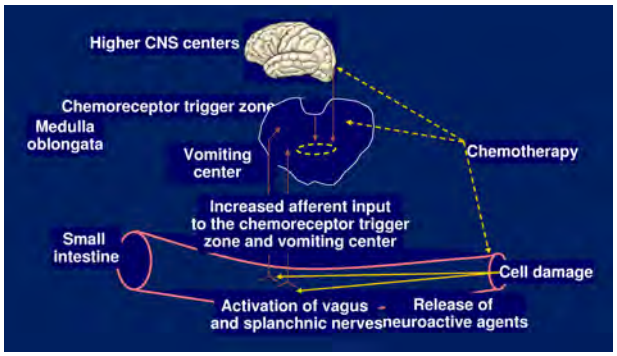

FIGURE 1 Proposed pathways of chemotherapy-induced emesis and nausea based on the assumption that the patient has a conscious awareness of unusual sensations in the brain stem's vomiting center.

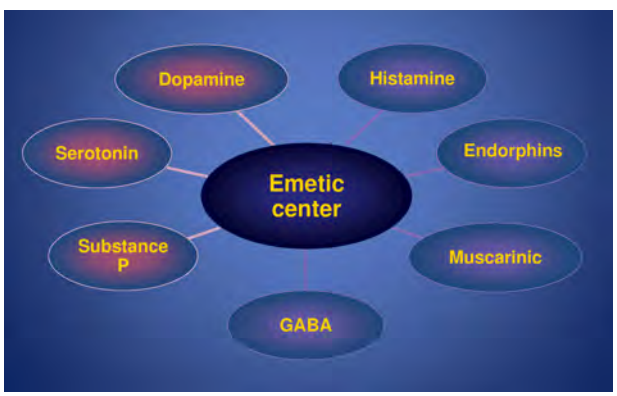

FIGURE 2 The receptors shown here are thought to be involved in CINV and are located in the periphery, such as the gastrointestinal tract, and in the central nervous system.

Figure 2 illustrates the various receptors that are considered to be involved in CINV. These receptors are located in the periphery, such as the gastrointestinal tract, and in the central nervous system (CNS). Various antiemetic agents have been developed as antagonists to the serotonin and the substance P receptors, with relative success in controlling emesis. It is not clear whether the serotonin and/or the substance P receptors are important in the control of nausea. Other receptors such as dopaminergic, histaminic, and muscarinic may be the dominant receptors in the control of nausea.[2]

Antiemetic agents

First-generation 5-HT_3 receptor antagonists

The 5-HT_3 receptor antagonists currently in use include the first-generation serotonin (5-HT_3) receptor antagonists dolasetron (Anzemet), granisetron, ondansetron, tropisetron,[10] azasetron,[11] and ramosetron.[12] They are considered equivalent in efficacy and toxicities when used in the recommended doses and have not been associated with major toxicities.[2] Azasetron and ramosetron are not available in North America and Europe and have not been compared extensively with the other 5-HT_3 receptor antagonists.

In 2006, Canada issued a drug alert for dolasetron, citing possible serious cardiovascular adverse events (cardiac arrhythmia) and stating that dolasetron was not indicated for the prevention of CINV in children but that it could be used for that indication in adults.[13] In 2010, the Food and Drug Administration (FDA) announced that the intravenous form of dolasetron should no longer be used to prevent CINV. New data suggested that dolasetron injection might increase the risk of developing a prolongation of the QT interval, which could precipitate life-threatening ventricular arrhythmia.[14]

The first-generation 5-HT_3 receptor antagonists have not been as effective against delayed emesis as they have been against acute CINV.[15–17] The first-generation 5-HT_3 receptor antagonists alone do not add significant efficacy to that obtained with dexamethasone in the control of delayed emesis.[16] Hickok et al[17] reported that the first-generation 5-HT_3 receptor antagonists used in the delayed period were no more effective in controlling nausea than was prochlorperazine. The antiemetic effects of prochlorperazine can be attributed to postsynaptic dopamine receptor blockade in the chemoreceptor trigger zone.

A meta-analysis showed that there was neither clinical evidence nor considerations of cost-effectiveness to justify using the first-generation 5-HT_3 antagonists beyond 24 hours after chemotherapy for the prevention of delayed emesis.[16] A number of recent studies have demonstrated that there has been poor control of delayed nausea by the first-generation 5-HT_3 receptor antagonists in patients receiving HEC or MEC[18-20] (Table 1). The use of granisetron and dexamethasone in patients receiving HEC resulted in "no nausea" in 25%-27% of patients.[19] The use of ondansetron plus dexamethasone in patients receiving MEC resulted in "no nausea" in 33% of patients and "no significant nausea" in 56% of patients.[20]

Second-generation 5-HT_3 receptor antagonists

Palonosetron, a second-generation 5-HT_3 receptor antagonist, has antiemetic activity at gastrointestinal sites and the CNS. Compared with the first-generation 5-HT_3 receptor antagonists, it has a higher potency, a significantly longer half-life, and a different molecular interaction with 5-HT_3 receptors.[21,22]

Animal studies have demonstrated that chemotherapy agents produce nausea and vomiting by releasing sub-

TABLE 1 Phase II and III trials of various agents for the treatment of chemotherapy induced nausea

Study	Chemotherapy	Phase	No. of patients	No Nausea, Delayed (%)	No Nausea, Overall (%)
Saito et al. [19]	HEC	III	1,114	Palo + Dex: 38 Gran + Dex: 27	Palo + Dex: 32 Gran + Dex: 25
Hesketh et al. [29]	HEC	III	1,043	—	Women: Aprepitant: 46 Control: 38 Men Aprepitant: 50 Control: 44
Warr et al. [20]	Cyclo + Doxo/Epi	III	866	Aprepitant: 37 Control: 36	Aprepitant: 33 Control: 33
Grote et al. [30]	MEC	II	58	APD: 31	APD: 30
Celio et al. [32]	MEC	III	334	Palo + Dex1: 57 Palo + Dex3: 62	Palo + Dex1: 52 Palo + Dex3: 57
Aapro et al. [33]	Cyclo + Doxo/Epi	III	300	Palo + Dex1: 50 Palo + Dex3: 55	Palo + Dex1: 47 Palo + Dex3: 50
Navari et al. [7]	MEC	II	32	OPD: 78	OPD: 78
Tan et al. [8]	MEC HEC	III III	229	OAD: 83* AD: 58 OAD: 70* AD: 30	OAD: 83* AD: 56 OAD: 70* AD: 28
Navari et al. [39]	HEC	III	257	OPD: 69* APD:38	OPD: 69* APD:38
Cruz et al. [42]	HEC	III	80	Gabapentin: 72 Control: 52	Gabapentin: 62 Control: 45
Meiri et al. [45]	MEC, HEC	III	61	No difference between dronabinol or ondansetron	Not reported

HEC = highly emetogenic chemotherapy; Palo = palonosetron; Dex = dexamethasone; Gran = granisetron; Cyclo = cyclophosphamide; Doxo = doxorubicin; Epi = epirubicin; MEC = moderately emetogenic chemotherapy; APD = aprepitant, palonosetron, dexamethasone; OPD = olanzapine, palonosetron, dexamethasone; OAD = olanzapine, azasetron, dexamethasone; AD = azasetron, dexamethasone.
* $P < .05$

stance P in the central nervous system and serotonin from the enterochromaffin cells of the small intestine. The released serotonin activates the 5-HT_3 receptors located on the vagal afferents to initiate the vomiting reflex. Palonosetron has demonstrated a 5-HT_3 receptor-binding affinity that is at least 30-fold higher than are other 5-HT_3 receptor antagonists.[21]

Rojas et al[22] recently reported that palonosetron exhibited allosteric binding and positive cooperativity when binding to the 5-HT_3 receptor rather than the simple bimolecular binding exhibited by granisetron and ondansetron. Additional studies by Rojas et al[22] suggested that palonosetron triggers 5-HT_3 receptor internalization and causes prolonged inhibition of receptor function. These differences in binding and effects on receptor function might explain some differences between palonosetron and the first-generation 5-HT_3 receptor antagonists.[3] A number of studies have shown a high level of efficacy and an excellent safety profile for palonosetron.[3,19,21,23–25] In subgroup analyses in single-dose trials, palonosetron appeared to control nausea better than did dolasetron[24] and ondansetron[25] in patients receiving MEC.

International antiemetic guidelines suggest the use of a 5-HT_3 receptor antagonist and dexamethasone before chemotherapy and dexamethasone after chemotherapy for patients receving MEC, and the use of a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant before chemotherapy and dexamethasone plus aprepitant after chemotherapy for patients receving HEC.[26–28] Based on recent studies, palonosetron has been recommended as the preferred 5-HT_3 receptor antagonist by multiple international antiemetic guidelines[27,28] for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC and HEC and for the prevention of delayed nausea and vomiting associated with initial and repeat courses of MEC.

Saito et al[19] conducted a comparison of palonosetron plus dexamethasone and granisetron plus dexamethasone for the prevention of CINV in patients receiving HEC. The palonosetron regimen provided a significantly higher CR and control of nausea, but neither regimen provided effective

control of nausea (no nausea; overall period: 31.9% palonosetron group; 25.0% granisetron group; Table 1).

There are no other second-generation 5-HT_3 receptor antagonists currently on the market, and there is no information available on other second-generation agents in development.

Aprepitant

Aprepitant is an NK-1 receptor antagonist that blocks the emetic effects of substance P.[4,5,18] When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT_3 receptor antagonist, aprepitant is effective in the prevention of CINV in patients receiving HEC.[5,18] This regimen is recommended in the guidelines of numerous international groups for the control of CINV in patients receiving HEC.[26-28]

Combined data from two large phase III trials of aprepitant plus a first-generation 5-HT_3 receptor antagonist and dexamethasone for the prevention of CINV in patients receiving HEC demonstrated an improvement in CR when aprepitant was added to ondansetron and dexamethasone. However, there was no improvement in nausea when the pooled data were analyzed for gender (no nausea, overall period: 46% for women, aprepitant group, 38% for women, control group; 50% for men, aprepitant group, 44% for men, control group)[29] (Table 1). The researchers used the same pooled data in a separate analysis, which[30] showed a statistical, but small, improvement in nausea with the use of aprepitant (no nausea, overall period: 48%, aprepitant group, 42%, control group; Table 1).

In a similar study of breast cancer patients receiving cyclophosphamide and doxorubicin or epirubicin, aprepitant was added to ondansetron and dexamethasone for the prevention of CINV. The addition of aprepitant to the 5-HT_3 receptor antagonist plus dexamethasone improved the CR, but there was no improvement in nausea (no nausea, overall period: 33% aprepitant group, 33% control group).[20]

Palonosetron and aprepitant have been combined with dexamethasone for the prevention of CINV in a phase II study of 58 patients who received doxorubicin and cyclophosphamide.[31] This three-drug antiemetic regimen was found to be safe and highly effective in preventing emesis and rescue in the acute, delayed, and overall periods, but there was poor control of nausea (no nausea, overall period: 30%; Table 1).

Dexamethasone

Dexamethasone is a corticosteroid that is used as an antiemetic and has been effective in controlling acute and delayed CINV, though there are concerns about its possible toxicity when it is used in multiple-day therapy to control CINV.[32] Patients receiving dexamethasone for prophylaxis for CINV reported moderate to severe problems with insomnia, hyperglycemia, indigestion, epigastric discomfort, agitation, increased appetite, weight gain, and acne.[32] Dexamethasone could be decreased or eliminated in an antiemetic regime if other agents effective in the acute and delayed periods are used.

Dexamethasone added to a 5-HT_3 receptor antagonist improves the control of acute CINV,[27-29] and it has been used as a single agent or in combination with other agents in an attempt to control delayed CINV.[26-28] The available studies show that dexamethasone alone, or in combination with a 5-HT_3 receptor antagonist or metaclopramide results in only a moderate reduction in delayed nausea.[18] As an antiemetic, metoclopramide acts as a dopamine antagonist, and its action raises the threshold of activity in the chemoreceptor trigger zone and decreases the input from afferent visceral nerves. High doses of metoclopramide have been found to antagonize 5-HT receptors in the peripheral nervous system in animals.[18]

Celio et al[33] used palonosetron in combination with 1 day or 3 days of dexamethasone to prevent CINV in patients receiving MEC. There was no improvement in CR (67.5% vs 71.1%; 1 day and 3 days, respectively) or no nausea (52.1% vs 56.5%; respectively) over the 5-day overall period. A similar study[34] using palonosetron plus dexamethasone for 1 day or 3 days for patients receiving MEC showed similar results: no improvement in CR (53.6% vs 53.7%) or in no nausea (47.0% vs 49.7%) over the 5-day overall period (Table 1).

Olanzapine

Olanzapine is an FDA-approved antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, D4 brain receptors; serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6 receptors; catecholamines at alpha1 adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H1 receptors.[35,36] Common side effects are sedation and weight gain,[37,38] as well as an association with the onset of diabetes mellitus.[39]

Sedation has not been observed with the doses administered for the prevention of CINV ($<$ 10 mg/day for 3 to 5 days).[6-8] Weight gain and the onset of diabetes are observed only when olanzapine is given at higher doses ($>$ 10 mg/day) for longer periods (daily for $>$ 3 months).[37-39]

Olanzapine's activity at multiple receptors, particularly at the D2, 5-HT_{2c}, and 5-HT_3 receptors, which appear to be involved in nausea and emesis, suggests that it may have significant antiemetic properties. A phase II trial demonstrated that olanzapine, when combined with a

single dose of dexamethasone and a single dose of palonosetron, was effective in controlling acute and delayed CINV in patients receiving both HEC and MEC.[7] There was excellent control of nausea in 32 patients receiving MEC (no nausea, overall period; 78%) without the use of multiple days of dexamethasone.

A phase III study showed that the addition of olanzapine to the 5-HT_3 receptor antagonist azasetron and dexamethasone improved delayed CINV in patients receiving HEC or MEC.[8] There was a significant improvement in nausea in the olanzapine group compared with the control group for patients receiving HEC (no nausea, overall period; 70% vs 28%) and MEC (no nausea, overall period; 86% vs 56%).

A phase III study randomized patients on HEC to receive olanzapine, palonosetron, dexamethasone (OPD) or aprepitant, palonosetron, dexamethasone (APD) for the prevention of CINV.[40] The CR rate was similar, but nausea was significantly improved in the OPD group (no nausea, overall period; 69% vs 38%). These results were consistent with the findings in the previous phase II and III studies using olanzapine, suggesting that olanzapine may be an effective and safe agent for the control of both emesis and nausea (Table 1).

Gabapentin

Gabapentin is a gamma-aminobutyric acid (GABA) analogue that has been used for the treatment of seizures, chronic neuropathic pain, and postherpetic neuralgia.[41] The mechanism of action exerted by gabapentin is unknown. Although gabapentin is structurally related to the neurotransmitter GABA, it does not interact with GABA receptors, is not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation.[41]

Guttuso et al[42] reported an improvement in CINV in six of nine breast cancer patients when gabapentin was used to prevent nausea. Cruz et al[43] added gabapentin to ondansetron, dexamethasone, and ranitidine to prevent CINV in patients receiving HEC. The CR rate was significantly improved in the patients receiving gabapentin, but nausea was not significantly improved (no nausea, overall period: 62% vs 45%; Table 1).

Cannabinoids

Studies with animal models have suggested that delta-9-tetrahydrocannabinoid (dronabinol) selectively acts on CB1 receptors in specific regions of the dorsal vagal complex to inhibit emesis.[44,45] Few reported studies have explored this mechanism in patients.[46,47] Meiri et al[46] looked at the efficacy of dronabinol versus ondansetron in patients receiving chemotherapy for a wide variety of neoplasms. Dronabinol and ondansetron were similarly effective antiemetic treatments in 61 patients receiving MEC and HEC.

Nabilone (Cesamet) is a synthetic cannabinoid, a racemic mixture of isomers, which mimics the main ingredient of cannabis (dronabinol). A review of the published English literature on the use of oral nabilone in the treatment of CINV concluded that cannabinoids do not add to the benefits of 5-HT_3 receptor antagonists.[47] Additional studies should be performed to determine the role of this drug class in the prevention or treatment of CINV.

Ginger

Ginger is an herbal supplement that has been used for reducing the severity of motion sickness, pregnancy-induced nausea, and postoperative nausea and vomiting.[48] The mechanism of action by which ginger might exert antiemetic effects is unclear. Animal studies have described enhanced gastrointestinal transport, anti–5-HT activity, and possible CNS antiemetic effects.[48] Experiments with human participants to determine the mechanism of action have shown varying results regarding gastric motility and corpus motor response.[48]

Pillai et al[49] added ginger to ondansetron and dexamethasone in children and young adults receiving HEC. They reported a reduction in the severity of acute and delayed CINV, but all of the patients had some nausea on days 1-4 after chemotherapy. Zick et al[50] reported that ginger provided no additional benefit in the reduction of the prevalence or severity of acute or delayed CINV when given with 5-HT_3 receptor antagonists and/or aprepitant in 162 cancer patients receiving chemotherapy. Ryan et al[51] gave ginger before and after chemotherapy to 644 patients and found a reduction in nausea during the first day of chemotherapy. The available studies do not support ginger as an effective agent for the prevention of chemotherapy-induced nausea.

Discusssion

The current data in the literature of multiple large studies suggest that neither the first or second generation 5-HT_3 receptor antagonists have been effective in the control of nausea in patients receiving either MEC or HEC, despite the marked improvement in the control of emesis. Similarly, aprepitant, the first NK-1 receptor antagonist to be used clinically for the prevention of CINV, is effective for the control of emesis but not nausea in patients receiving MEC or HEC.

These studies suggest that the serotonin (5-HT_3) and the substance P (NK-1) receptors may not be the important receptors in the mediation of nausea, despite their important role in chemotherapy induced emesis.

The recent phase II and phase III studies using olanzapine suggest that this might be an important agent in the control of chemotherapy-induced nausea. Olanzapine is known to affect a wide variety of receptors including dopamine D2, 5-HT_{2C}, histaminic, and muscarinic receptors. Any or all of these receptors may be the mediators of chemotherapy induced nausea.

Preliminary small studies with gabapentin have demonstrated some effectiveness in the control of chemotherapy-induced emesis, but the control of nausea remains to be determined. More studies with the use of cannabinoids need to be performed before it is known whether this class of agents is clinically efficacious in the control of CINV. Studies to date do not support the use of ginger as an effective agent in the prevention of CINV.

Conclusions

It is apparent that the commonly used antiemetics are not effective for the control of chemotherapy-induced nausea, despite their recent success in the control of emesis. New studies using novel agents and nausea as the primary endpoint need to be performed. At this point, olanzapine appears promising for the control of both emesis and nausea in patients receiving MEC or HEC.

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