# Management of chemotherapy-induced nausea and vomiting

***Chemotherapy-induced nausea and vomiting are symptoms that cause major concern to oncology patients. This article explores the types of nausea and vomiting in the context of chemotherapy, and discusses their pathogenesis and management.***

Chemotherapy-induced nausea and vomiting (CINV) are the symptoms causing most concern to patients on chemotherapy (Coates et al, 1983). These symptoms can seriously impair the patient's quality of life (Bliss et al, 1992). Serious complications can arise such as dehydration, electrolyte imbalance, anorexia with subsequent weight loss, wound dehiscence and Mallory–Weiss oesophageal tears. In addition, patients may refuse further chemotherapy (Ritter Jr et al, 1998).

## Types of CINV

There are a number of different types of nausea and vomiting which can affect patients on chemotherapy. These include:

- Acute nausea/vomiting: occurring within 24 hours of therapy. This can be subdivided into acute (within 12 hours) and late-acute (between 12 and 24 hours).
- Delayed nausea and vomiting: commencing more than 24 hours after administration of chemotherapy. May persist for 6–7 days
- Anticipatory nausea and vomiting: occurring before chemotherapy administration
- Breakthrough nausea and vomiting: occurring despite anti-emetic prophylaxis and/or necessitating the use of rescue medication
- Refractory nausea and vomiting: occurring during subsequent treatment cycles when control was incomplete in earlier cycles.

## Risk factors for CINV

Some patients are at high risk for developing CINV (Doherty, 1999). These include:

- Females
- Those with a prior history of motion sickness
- Those with a prior history of pregnancy-induced emesis
- Those with high anxiety levels
- Those with poorly controlled nausea and vomiting in previous cycles of chemotherapy
- Those with an alcohol consumption <10 units/week.

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## Emetogenic potential of chemotherapeutic agents

Chemotherapeutic agents vary in their potential for causing emesis and are grouped into five categories varying from very high to very low emetogenic potential (*Table 1*) (Hesketh et al, 1997). This categorization helps establish appropriate antiemetic therapy for patients based on the likelihood of developing nausea and vomiting.

## Pathophysiology of nausea and vomiting

Administration of chemotherapy leads to formation of free radicals. These free radicals stimulate enterochromaffin cells in the intestine causing a release of 5-hydroxytryptamine (5-HT, serotonin). The released 5-HT stimulates 5-$HT_3$ receptors on abdominal vagal afferent neurons. These neurons terminate directly beneath the area postrema in the nucleus tractus solitarius, which when stimulated, produces symptoms of nausea and vomiting (Lindley and Blower, 2000).

Substance P is also released from the intestine in response to chemotherapy. Substance P stimulates neurokinin-1 (NK-1) receptors to produce nausea and vomiting. NK-1 receptors are located in intestine, chemoreceptor trigger zones and the nucleus of tractus solitarius in brain.

Substances that play a lesser role in mediating an emetic response to chemotherapy include histamine, acetylcholine, γ-aminobutyric acid (GABA) and endorphins.

Other factors contributing to nausea and vomiting are:

- Alterations of taste and smell
- Psychogenic mechanisms
- Pre-existing conditions such as brain metastases, intestinal obstruction, metabolic abnormalities like hyponatraemia, hyperglycaemia and hypercalcaemia
- Emetogenic potential of chemotherapy.

## Drugs used in management of CINV

Pharmacological agents used in the management of CINV are classified into the following types:

- 5-$HT_3$ receptor antagonists
- Corticosteroids
- Dopaminergic receptor antagonists
- Substance P antagonists (NK-1 receptor antagonists)

- Cannabinoids
- Benzodiazepines
- Substituted benzamides (metoclopramide)
- Butyrophenones
- Phenothiazines
- Histamine antagonists
- Combined dopaminergic and 5-$HT_3$ receptor antagonists.

The doses used in acute and delayed CINV are summarized in *Table 2*.

5-$HT_3$ receptor antagonists, corticosteroids and NK-1 receptor antagonists are the most effective and widely used forms of antiemetics.

## 5-$HT_3$ antagonists

5-$HT_3$ antagonists prevent nausea and vomiting by blocking the action of 5-$HT_3$ on vagal afferents to the vomiting centre in the brain. 5-$HT_3$ antagonists may also have a direct action mediated through blockade of serotonin action in the brain centres.

5-$HT_3$ antagonists in combination with corticosteroids are considered the gold standard for management of nausea and vomiting in oncology patients (Aapro and Blower, 2005).

Ondansetron, granesetron and palonosetron are members of this class. Their efficacy is equivalent; however, palonosetron has a long half life of 40 hours which permits a single intravenous dose half an hour before chemotherapy.

Important adverse effects include headache, constipation, diarrhoea, elevation of liver enzymes, allergic reactions including anaphylaxis, bradycardia, hypotension and atrioventricular block.

## Corticosteroids

The exact antiemetic mechanism is not understood but corticosteroids possibly act through modification of prostaglandin activity in the brain. Dexamethasone and methylprednisolone are the most frequently used antiemetic corticosteroids. Adverse effects include depression, psychosis, diabetes, peptic ulceration, adrenal suppression and suppression of signs of infection. These adverse effects are rarely of major concern with short-term use.

## Dopamine receptor antagonists

### Substituted benzamides

Metoclopramide prevents nausea and vomiting through blocking dopaminergic ($D_2$) receptors. It also has a mild antagonistic effect on 5-$HT_3$ receptors. Adverse effects include rashes and allergies, extrapyramidal effects, drowsiness, restlessness, diarrhoea, hyperprolactinaemia, and neuroleptic malignant syndrome.

### Butyrophenones

Butyrophenones are also $D_2$ receptor antagonists. Significant adverse effects include extrapyramidal effects, akathisia, hypotension and sedation.

**Table 1. Emetogenic potential of some chemotherapeutic agents**

| | |
|---|---|
| Very high frequency > 90% | Cisplatin |
| | Dacarbazine |
| | Streptozotocin |
| | Cyclophosphamide 1000 mg/m$^2$ |
| | Lomustine |
| High frequency 60–90% | Cyclophosphamide ≥ 600 mg/m$^2$ |
| | Methotrexate ≥ 1000 mg/m$^2$ |
| | Carboplatin |
| | Ifosfamide |
| | Busulphan high dose |
| | Doxorubicin >60 mg/m$^2$ |
| | Irinotecan |
| | Cisplatin |
| Moderate frequency 30–60% | Aldesleukin * |
| | Cyclophosphamide < 600 mg/m$^2$ |
| | Doxorubicin ≤ 40 mg/m$^2$ |
| | Epirubicin |
| | Methotrexate < 1000 mg/m$^2$ |
| | Procarbazine |
| Low frequency 10–30% | Docetaxel |
| | Etoposide |
| | Fluorouracil |
| | Gemcitabine |
| | Paclitaxel |
| | Topotecan |
| Very low frequency< 10% | Bleomycin |
| | Busulfan |
| | Chlorambucil |
| | Hydroxyurea |
| | Vinblastine |
| | Vincristine |
| | Vinorelbine |

* corticosteroids are not indicated in prophylaxis with aldesleukin

### Phenothiazines

Phenothiazines act mainly by blocking dopamine action on chemoreceptor trigger zones. Prochlorperazine and methotrimeprazine are members of this class. Adverse effects are extrapyramidal reactions, sedation, hypotension, hypothermia and neuroleptic malignant syndrome.

## NK-1 receptor antagonists

NK-1 receptor antagonists block the central action of substance P released from the intestine in response to chemotherapy (Rittenberg, 2002). Aprepitant is an agent of this class that is given in conjunction with cortico-steroids and 5-$HT_3$ antagonists to prevent nausea and vomiting after

highly emetogenic regimens. It is also administered to selected patients receiving moderately emetic regimens.

In two multicentre studies receiving cisplatin-based chemotherapy, aprepitant with standard ondansetron and dexamethasone was found to be significantly more efficacious than standard therapy alone. The complete response to standard therapy with or without aprepitant was 72.7% *vs* 52.3% in one study (Hesketh et al, 2003) and 62.7% *vs* 43.3% in another (Poli-Bigelli et al, 2003).

### Cannabinoids

Cannabinoids act via central mechanisms to give a feeling of euphoria, altered sensations and memory loss. Adverse effects include acute withdrawal syndrome, sedation, dry mouth, orthostatic hypotension, dizziness and ataxia.

### Benzodiazepines

Lorazepam and alprazolam are used in conjunction with other antiemetics and are effective particularly in anticipatory nausea and vomiting. Adverse effects include drowsiness, light-headedness, confusion and ataxia, dependence and paradoxical increase in aggression.

### Antihistamines

Cyclizine is an antihistamine which is useful for breakthrough nausea and vomiting. It has anticholinergic activity and can precipitate glaucoma. Adverse effects are drowsiness, dryness of the mouth, nose and throat, blurred vision, tachycardia, urinary retention, constipation, restlessness, nervousness, insomnia, and auditory and visual hallucinations.

### Serotonin–dopamine antagonists

Olanzapine is classified as an atypical antipsychotic with selective antagonististic activity at 5-HT, dopamine, muscarinic, histamine $H_1$, and adrenergic $\alpha 1$ receptors.

In one phase II trial olanzapine has been shown to achieve good control of acute and delayed emesis when given in conjunction with granisetron and dexamethasone. All patients in this study received cyclophosphamide, doxorubicin, and/or cisplatin chemotherapy (Navari et al, 2004).

Adverse effects are postural hypotension, bradycardia, seizures, neuroleptic malignant syndrome, tardive dyskinesia and transaminase elevation.

## Recommendations for prevention of CINV

Various guidelines are available for the prevention of CINV. These come from sources such as the European Society for Medical Oncology (Herrstedt et al, 2005), the American Society of Clinical Oncology, (Gralla et al, 1999), the Multinational Association of Supportive

**Table 2. Pharmacological management of acute and delayed chemotherapy-induced nausea and vomiting**

| | | Schedule for acute chemotherapy-induced emesis | Schedule for delayed/ breakthrough emesis |
|---|---|---|---|
| Serotonin receptor antagonists | Granisetron | 1 mg or 0.01 mg/kg iv once before chemotherapy | |
| | Granisetron | 2 mg po once before chemotherapy | |
| | Ondansetron | 8 mg or 0.15 mg/kg iv once before chemotherapy | |
| | Ondansetron | 12–24 mg/d po once before chemotherapy | 12–24 mg/d po in two to three divided doses |
| | Palonosetron | 0.25 mg iv once before chemotherapy over 30 seconds approximately 30 minutes before chemotherapy | |
| Corticosteroids | Dexamethasone | 20 mg iv once before chemotherapy | |
| | Methylprednisolone | 40–125 mg once before chemotherapy | |
| Dopamine receptor antagonists | Metoclopramide | 2–3 mg/kg iv before chemotherapy and 2 hours after chemotherapy | 20 mg to 0.5 mg/kg po bd–tds |
| | Methatrimeprazine | | 12.5–50 mg 4–8-hourly |
| | Prochlorperazine | | 5–10 mg bd–tds |
| | Haloperidol | | 1–2 mg po 4–6-hourly or 1–3 mg iv 4–6-hourly |
| Substance P/Neurokinin 1 (NK1) receptor antagonist | Aprepitant | 125 mg po1 hour before chemotherapy treatment | |
| | | 80 mg po once daily in the morning on days 2 and 3 | |
| Cannabinoids | Nabilone | | 1–2 mg bd |
| | Dronabinol | | 5 mg po tds–qds |
| Benzodiazepines | Alprazolam | 0.5–2 mg po tds on the night before treatment | |
| | Lorazepam | 0.5–2 mg po on night before and morning of treatment | 0.5–2 mg po 4–6-hourly |
| Antihistamines | Cyclizine | | 50 mg tds |
| Serotonin–dopamine antagonists | Olanzapine | | 2.5–5 mg po bd |

bd = twice daily; iv = intravenous; po = per oral; qds = four times a day; tds = three times a day

Care in Cancer (www.mascc.org), the National Cancer Institute (www.nci.nih.gov/), and the National Comprehensive Cancer Network (2006).

*Table 3* demonstrates the usual therapy for prevention of CINV.

## Alternative therapies

### Acupuncture and acupressure

Acupuncture techniques act through hypophyseal secretion of beta-endorphins and adrenocorticotropic hormone, with subsequent inhibition of the chemoreceptor trigger zone and vomiting centres (Samuels, 2003).

These techniques are safe and are sometimes used in conjunction with pharmacotherapy (Collins and Thomas, 2004).

### Hypnosis, behavioural intervention and distraction techniques

All the above techniques have been used as an adjunct to pharmacological therapy (Troesch et al, 1993; Marchioro et al, 2000).

## Conclusions

CINV arises via complex pathological processes. Understanding these processes has lead to the development of highly effective therapies. As newer pharmacological agents are being developed patients are able to be free from nausea and vomiting during their course of chemotherapy and hence lead a better quality of life. BJHM

*Conflict of interest: none.*


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**Table 3. Schedules for prevention of chemotherapy-induced nausea and vomiting**

| | | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|---|
| High emetic risk | Aprepitant | 125 mg | 80 mg | 80 mg | None |
| | Dexamethasone | 12 mg po | 8 mg po | 8 mg po | 8 mg po |
| | Ondansetron | 32 mg iv | none | none | none |
| Moderate emetic risk | Day 1<br>Dexamethasone 12 mg po or iv and 5-HT3 antagonist<br>Days 2–4<br>Dexamethasone 8 mg po or iv daily or 4 mg po or iv bd or $5\text{-HT}_3$ antagonist or metoclopramide 0.5 mg/kg po or iv 6-hourly or 20 mg po four times daily | | | | |
| Low emetic risk | Dexamethasone 12 mg po or iv daily or metoclopramide 20–40 mg po 4–6-hourly or 1–2 mg/kg iv 3–4-hourly | | | | |
| Minimal emetic risk | No routine prophylaxis | | | | |

$5\text{-HT}_3$ = 5-hydroxytryptamine 3; bd = twice daily; iv = intravenous; po = per oral

## KEY POINTS

- Nausea and vomiting are symptoms of significant importance to the patients.
- Control of these symptoms is necessary for prevention of complications and assurance of patient compliance.
- Neurokinin-1 (NK-1) receptor antagonists, 5-hydroxytryptamine 3 ($5\text{-HT}_3$) antagonists, metoclopramide and corticosteroids form the basis of chemotherapy-induced nausea and vomiting prevention.
- Antihistamines, dopamine receptor blockers, and cannabinoids are useful in prevention and treatment of delayed nausea and vomiting.
- Benzodiazepines are useful for anticipatory nausea.
- With current strategies and pharmacotherapy, it is possible to keep patients entirely symptom free, even with highly emetogenic chemotherapy regimens.
- In spite of adequate antiemetic cover, some patients may require breakthrough medication.