The use of cytotoxic drugs such as cisplatin, which caused severe nausea and vomiting unresponsive to standard antiemetics, stimulated research into the mechanisms of nausea and vomiting. Cisplatin was associated with both an acute emesis in the first 24 hours and a delayed emesis which could last for a week. The discovery of that 5 hydroxytryptamine3 receptors in the small intestine and brain were responsible for acute chemotherapy induced vomiting and the introduction of 5-HT3 receptor antagonists revolutionised the treatment of acute chemotherapy induced emesis, but had only minor impact on delayed emesis, which was thought to be mediated by a different mechanism. Now aprepitant a new drug that is a 5-HT3 receptor antagonist, which is centrally acting and given orally, has improved the control of acute emesis when added to a 5-HT3 antagonist and dexamethasone, but more importantly has made a major advance in the control of delayed emesis when continued for two further days in combination with dexamethasone. This control of nausea and vomiting associated with chemotherapy has translated into improved quality of life of the patients receiving chemotherapy.

Nausea and vomiting have been listed by patients as amongst the most distressing side effects of chemotherapy. Much of the knowledge gained over the last two decades about the mechanisms of emesis has resulted from the need to control chemotherapy induced emesis following the introduction of cytotoxic drugs of high emetic potential, such as cisplatin.

There are three phases of emesis associated with chemotherapy. Following cisplatin, which is the cytotoxic used in trials of new antiemetics because without antiemetics it causes emesis in most patients, there is an acute phase of emesis starting a few hours after chemotherapy and lasting until 18 to 24 hours, then a delayed phase, which follows and can last for up to a week. Finally there is anticipatory nausea and vomiting which is a conditioned response prior to the chemotherapy in subsequent cycles when emesis has occurred with previous doses. This provides the rationale for prophylactically trying to prevent post chemotherapy emesis so there can be no learned response.

**Early Drugs Used For Emesis**

The initial anti-emetic drugs used for chemotherapy induced emesis were dopamine antagonists, particularly metoclopramide, which blocked the D2 receptor thought to mediate emesis. At conventional doses this drug was not very effective, however a breakthrough came when, based on animal studies, clinical trials established that high doses of metoclopramide, up to 3mg/kg were more effective for preventing cisplatin induced emesis and were tolerated with only sporadic extrapyramidal reactions. It is now believed that high-dose metoclopramide affects the 5 hydroxytryptamine-3 (5HT3) receptor.

Other drugs available at the time included prochlorperazine, where again low doses were minimally effective and higher doses more so, but at the expense of toxicities such as hypotension and extrapyramidal reactions. Of the butyrophenones, oral domperidone has been most used, particularly when extrapyramidal reactions prevent the use of prochlorperazine and metoclopramide. Even cannabinoids were tried because of anecdotal reports from young patients who smoked marijuana that it alleviated their vomiting after chemotherapy. Delta-9-tetrahydrocannabinol was less active than high-dose intravenous metoclopramide in controlling cisplatin-induced emesis, but is better with chemotherapy of moderate emetic potential as are the synthetic cannabinoids levonantradol and nabilon. They are, however, more toxic than other antiemetics with the somnolence and dysphoric reactions tolerated poorly, particularly in older patients.

**Co-Administered Drugs**

The empirical observation that chemotherapy cycles including a corticosteroid were associated with less emesis than those without led to these agents being investigated as antiemetics. Although they have some efficacy as single agents their greatest role has been as part of antiemetic combinations.

Benzodiazepines such as lorazepam have been used in addition to antiemetics, particularly metoclopramide and prochlorperazine. Lorazepam has an amnesic anxiolytic effect and is a sedative. This can improve the patients’ tolerance of chemotherapy and can reduce the risk of extrapyramidal reactions from metoclopramide. Trials of benzodiazepines have been directed at reducing anticipatory emesis.

**5-Hydroxytryptamine3 Receptor Antagonists**

It was the discovery that cisplatin-induced acute emesis could be ameliorated by specifically blocking one of the seven 5-hydroxytryptamine (5-HT) receptors, the 5-HT3 receptor, that allowed a great stride in our understanding of the pathways of the emetic response. The 5-HT3 receptors are found centrally and peripherally where the main site of activity is in the small intestine. The 5-HT3 receptors have allowed identification of the role of the vagal afferent-enterochromaffin cell unit in the emetic response. Cytotoxic drugs cause a calcium dependent release of hydroxytryptamine from enterochromaffin cells in the upper gastrointestinal mucosa. This is reflected by the fact that cisplatin-induced emesis is associated with increases in urine and plasma 5-hydroxyindoleacetic acid (5 HIAA), a metabolite of 5-HT supposedly released from the enterochromaffin cells. It is an anomaly, however, that cyclophosphamide induced emesis which responds to 5-HT3 antagonists fails to induce these changes to 5-HT release and so the precise mechanism of emesis remains undefined.

The recognition of the role of the 5-HT3 receptor in acute post chemotherapy emesis and the development of selective antagonists including ondansetron, granisetron, tropisetron and dolasetron has revolutionised the management of this complication of anti-cancer chemotherapy. They are not broad spectrum antiemetics, their major uses being confined to post chemotherapy and post anaesthetic emesis. Despite preclinical differences, there is little difference clinically between the drugs.

The 5-HT3 receptor antagonists were shown to be superior to high dose metoclopramide regimes for preventing chemotherapy-induced emesis and they have a favorable toxicity profile with reversible headache, constipation and mild elevations in liver transaminases being the most common side effects.

A 5-HT3 receptor antagonist combined with dexamethasone had become the gold standard given prophylactically to prevent acute post chemotherapy induced emesis. This results in complete...
Acute and delayed cisplatin-induced emesis 

As a class of drugs, clinically there is a threshold effect for efficacy, only a modest dose response curve and a plateau in therapeutic efficacy. Failure of response or breakthrough of emesis on these agents may not be remedied by larger or more frequent dosing because other receptor mechanisms may be responsible. Current single daily dosage regimens are most commonly used. Oral doses when adjusted for their bioavailability seem as effective as intravenous dosing if there are no barriers to absorption. Mainly used intravenously and orally, other formulations such as ondansetron wafers, which dissolve in the mouth and suppositories have been trialed.

Delayed Emesis

The 5-HT<sub>3</sub> receptor antagonists were very effective for acute emesis, but a second mechanism of emesis was responsible for delayed emesis which begins towards the end of the first day and can continue for a week. If a 5-HT<sub>3</sub> antagonist and dexamethasone was continued the control of the delayed phase of emesis rarely exceeded 50 per cent. Here dexamethasone appeared to be the key drug and combining it with metoclopramide yielded similar results to studies combining it with 5-HT<sub>3</sub> antagonists. It is now known that the centrally located neurokinin1(NK1) receptors are important mediators of delayed post chemotherapy emesis.

Neurokinin<sub>1</sub>: Receptor Antagonists

 Substance P is an 11 amino acid neurotransmitter which displays a strong affinity for the NK<sub>1</sub> receptor. There are high concentrations of substance P which can be imaged by positron emission tomography, in areas of the brain responsible for emesis such as the nucleus tractus solitarius and area postrema. NK<sub>1</sub> receptor antagonists are highly selective for NK1 receptors and they act centrally, inhibiting the binding of substance P. In the ferret model they show activity against both acute and delayed cisplatin-induced emesis.

The first of the NK<sub>1</sub> antagonists available clinically is aprepitant. It has a pro-drug L-758298, which is an intravenous preparation, but itself is an oral formulation with 60 to 65 per cent being absorbed and that absorption not affected by food. It is recommended for once a day administration. It crosses the blood brain barrier which is necessary for its antiemetic effect. Its main pathway of elimination is by the cytochrome P450 CYP3A4 isozyme of which it is a moderate inhibitor. This creates the potential for drug interactions. Of significance, when given with dexamethasone there was a two fold increase in dexamethasone AUC (area under the dose/time curve). The AUC of ethinyl estradiol is decreased by 40 per cent and the manufacturer recommends alternate methods of contraception. No significant interactions have been found with 5-HT<sub>3</sub>: receptor antagonists or cytotoxics such as docetaxel. No dosage adjustments are necessary for mild to moderate hepatic or renal insufficiency, age race or gender. Based on negligible pharmacokinetic differences, there are no dosage adjustments recommended on the basis of age, race or gender. PET studies have shown correlations between receptor occupancy and plasma concentration and efficacy. Antiemetic efficacy increases with increased receptor occupancy up until a dose of 125mg but no additional benefit is seen with higher doses.

The single agent activity of these agents was disappointing against acute cisplatin-induced emesis and therefore the NK<sub>1</sub> receptor antagonists have been trialed added to 5-HT<sub>3</sub> receptor antagonists and steroids. Following phase I studies there were five phase II trials (two with the produg and three with aprepitant) in cisplatin induced emesis, which suggested additive activity in controlling acute emesis and good control of delayed emesis if the three drugs were given on day one (either granisetron or ondansetron with dexamethasone and aprepitant) and the dexamethasone and aprepitant on days 2 and 3.

The first phase III placebo controlled trials were performed in South America (Poli-Bigelli et al) and in centers from North America, Europe and Australia (Hesketh et al). Both studies included patients receiving their first cycles of cisplatin >70mg/m<sup>2</sup>. The patients on the standard arms of both studies received intravenous ondansetron 32mg 30 minutes before cisplatin with oral dexamethasone 20mg on day one followed by oral dexamethasone 8mg twice daily from days two to four. The aprepitant groups received oral aprepitant 125mg one hour before cisplatin, then intravenous ondansetron 32mg 30 minutes before cisplatin with oral dexamethasone 12mg on day one. On days two and three oral aprepitant 80mg and oral dexamethasone 8mg only once daily (because of the interaction with dexamethasone) was given and then day four oral dexamethasone 8mg. An extension phase of the study evaluated courses two to six.

Combining trials 1099 patients were enrolled. The complete response rate for the days of the first cycle in the Poli-Bigelli trial was 62.7 per cent for the aprepitant group versus 43.3 per cent for control (p<0.001) and for the Hesketh trial 72.7 per cent aprepitant versus 52.3 per cent control (p<0.001). For acute emesis the results were aprepitant 82.8 per cent versus control 68.4 per cent (p<0.001), for Poli-Bigelli and aprepitant 89.2 per cent versus controls 78.1 per cent (p<0.001) for Hesketh. The biggest differences were seen in delayed emesis; 67.7 per cent versus 46.8 per cent (p<0.001) and 74.4 per cent versus 55.8 per cent (p<0.001) respectively. Similar results were seen with nausea. The efficacy of aprepitant was maintained over six courses as was consistent with the result of a study designed to specifically test protection over multiple cycles.

In the two phase III trials logistic regression analyses of the Functional Living Index Emesis (FLIE) quality of life scale showed that more patients in the aprepitant groups reported minimal or no impact of chemotherapy induced nausea and vomiting on their daily life compared to those on the standard treatments (74.7 per cent versus 63.5 per cent in Poli-Bigelli and 70.4 per cent versus 64.3 per cent in Hesketh). Moreover this result was independent of the gender of the patients. In the Hesketh study, the percentage of males (69.8 per cent) and females (77.6 per cent) with complete response overall were similar in the aprepitant treated group, but in the standard arm complete responses were less for females (38.8 per cent) than males (60.5 per cent), which is the more usual result since females don’t respond to other antiemetics as well as males.

Aprepitant added to a 5HT<sub>3</sub>: receptor antagonist and dexamethasone was effective in both the older and younger age groups, whereas other antiemetics tend to be less effective in younger patients. The overall complete response in patients aged 65 and over was 76 per cent for the aprepitant arm and 54 per cent for the standard arm (p<0.001). Similar results are seen for both the acute and delayed phases of emesis and safety comparisons between older and younger patients showed no difference. The FLIE analysis also showed that the addition of aprepitant to standard therapy reduced the impact of post chemotherapy emesis on both older and younger patients.

Aprepitant was well tolerated. The incidence of drug related adverse events was 19.5 per cent for aprepitant versus 14.4 per cent controls on Poli-Bigelli and 14.6 per cent versus 11.0 per cent on Hesketh. Anorexia, asthenia and hiccoughs were more...
frequent with aprepitant; the other side effects were similar to the 5HT3 antagonists with which they were combined.

**Conclusions**

The new standard for antiemetic prophylaxis for drugs of high emetic potential will be a 5HT3 receptor antagonist, dexamethasone and aprepitant for the acute phase followed by aprepitant and dexamethasone for two days of the delayed phase of emesis. Traditionally, with cytotoxics of moderate emetic potential, similar antiemetic regimens are used to those used with drugs of high emetic potential, although one of the newer HT3 receptor antagonists, palonosetron, has been specifically given an indication for use for delayed emesis in this setting. Studies are ongoing to evaluate combinations including the NK1 receptor antagonists for cytotoxics of moderate emetic potential and see whether delayed emesis will be as well controlled in this setting as it is when used with cytotoxics of high emetic potential.

Finally in the era of more targeted therapy, the emergence of gene array technology identifying the genes coding for the 5HT3 and NK1 receptors may allow clinical correlations and more rational selection of antiemetic regimens for patients. For example, patients with genetic variations in the 5HT3B receptor gene might respond differently to antiemetic treatments including the 5-HT3 receptor antagonists.

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