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Anti-emesis with Cancer Chemotherapy

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Advances in supportive care have been among the most influential changes in cancer treatments over the past few years. Effective anti-emetic therapy has markedly reduced suffering due to emesis and has allowed most chemotherapy to be delivered on an outpatient basis. Carefully designed studies have combined knowledge of clinical aspects of chemotherapy treatment with relevant neuropharmacological considerations. This has permitted the continued development of new agents and combination regimens, resulting in better emetic control with fewer side-effects and optimal patient and staff convenience. Today, the most extensively used anti-emetic agents for patients receiving moderately to severely emetogenic chemotherapy are the 5-hydroxytryptamine ($5\text{-}HT_3$) receptor antagonists. Currently available agents in this therapeutic class include ondansetron, granisetron, and tropisetron; dolasetron, another member of this class, is available in the U.K. and is now approvable in the U.S.A. Use of the best proven regimens prevents both acute and delayed emesis in most patients. In patients receiving cisplatin, 75–85% achieve complete control of acute emesis and 50–75% have complete control of delayed emesis. In patients receiving moderately emetogenic chemotherapy, complete control of acute emesis is achieved by 90% of patients and complete control of delayed emesis by 80–95% of patients. The most effective and convenient regimens for acute emesis employ a combination of serotonin antagonists with corticosteroids, single-dose schedules, the lowest effective doses and, most recently, oral administration. Further improvement of emetic control will require more widespread adherence to the best established regimens and identification of other pharmacological pathways. © **1997 Published by Elsevier Science Ltd.**

Key words: anti-emetic therapy, cancer, chemotherapy, corticosteroid, emesis, 5-hydroxytryptamine ($5\text{-}HT_3$) antagonist, serotonin antagonist, supportive care
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INTRODUCTION

IMPROVING THE control of chemotherapy-induced emesis continues to be a major goal in supportive care and in the treatment of cancer. Emesis can now be prevented in most patients, and the severity of emesis has been greatly reduced in patients who were refractory to older anti-emetic regimens. Although much progress has been made in anti-emetic therapy, complete control of emesis has not been achieved in all settings.

To assess possibilities for further improvement of emesis, a full understanding of the methods and degree of current control is needed. Appreciation of the current degree of progress requires an understanding of the neuropharmacology of emesis, the identification of effective anti-emetics, and the use of established research methodologies. The purpose of this paper is to outline advances, areas of concern, and potential methods for enhancing the control of emesis.

CONTROLLING CHEMOTHERAPY-INDUCED EMESIS

The major emetic problems associated with chemotherapy are acute, delayed, and anticipatory emesis. Of these, the best studied and controlled is acute emesis. Using currently available anti-emetics, complete control rates of 75–90% have been achieved (Table 1). This rate is in marked contrast to control rates of < 1–20%, depending on thetype of chemotherapy, that prevailed in the early 1980s [1–3].

The principles involved in addressing the problem of chemotherapy-induced emesis include: (1) selection of the most active agents; (2) administration of combination anti-emetic therapy using a serotonin type 3 ($5\text{-}HT_3$) antagonist and a corticosteroid; and (3) use of the most effective doses and schedules with minimisation of side-effects. Applying these convenient and cost-saving methods is mandatory if optimal control of emesis is to be achieved.

Table 1. Summary of progress and problems in controlling emesis in oncology

Type of emesis	Clinical situation	Comments
Acute	Complete control with cisplatin	≥75–85% control with combination regimens
	Complete control with moderate-risk agents	≥90% control with combination regimens
	Complete control with low-risk agents	≥95% control with oral corticosteroids
	Consecutive day treatment	Poorer control, few well-conducted studies, problems of delayed and anticipatory emesis
	High-dose chemotherapy or bone-marrow transplantation	Poorer control, few well-conducted studies, problem of radiotherapy-induced emesis in many instances
	Radiotherapy	Overall, less of a problem than with chemotherapy, problem of consecutive-day treatment, few well-controlled studies
	Paediatrics	5-HT_3 antagonists effective, doses and schedules not well defined, few well designed studies
Delayed	Complete control	Improvements needed, corticosteroids effective and corticosteroids + metoclopramide are superior. Role of 5-HT_3 antagonists unclear, but probably not more effective than metoclopramide + corticosteroids and markedly more expensive
Anticipatory	Prevention	Cornerstone of treatment, should use best regimens for acute and delayed emesis
	Treatment	Some efficacy with behaviour therapy techniques. Benzodiazepines may be helpful
General considerations	Side-effects	Low; easily managed with 5-HT_3 antagonists and with combination regimens
	Convenience/flexibilty	High; single-dose regimens are best, regimens are easily applied to inpatient or outpatient settings; all-oral regimens are likely to enhance convenience
	Cost	Moderate to high; savings achievable by using effective lower dose regimens, single dosing, and oral regimens. Following these principles can lower cost dramatically without affecting efficacy

ANTI-EMETIC AGENTS

Metoclopramide [2, 3] was the first 5-HT receptor antagonist anti-emetic, although it was not originally identified as working by that mechanism. Metoclopramide also affects dopamine receptors, but at high doses its efficacy is probably mediated by blocking 5-HT_3 receptors. With the development of the selective 5-HT_3 receptor antagonists, more specific treatment with fewer side-effects and greater convenience became the standard. Studies comparing metoclopramide regimens with different selective 5-HT_3 antagonists showed similar or superior efficacy for the later agents [4]. This efficacy, coupled with the more convenient use of 5-HT_3 antagonists and a low side-effect profile, made these newer agents the treatment of choice for patients receiving moderately to severely emetogenic chemotherapy.

The selective 5-HT_3 antagonists differ in terms of their structures, potencies per milligram, and pharmacokinetic profiles. However, their respective efficacies, mechanisms of action, and clinically important side-effects are essentially identical. The most familiar of these agents are granisetron, ondansetron, and tropisetron, all of which are currently available in many countries. Dolasetron is available in the U.K. and is now approvable in the U.S.A. Several prospective, randomised comparison trials have shown equivalence between ondansetron and granisetron [5], as well as between ondansetron and dolasetron [6], and granisetron and dolasetron [7]. The same level of efficacy has been demonstrated among these agents.

All of these compounds are associated with a low incidence of side-effects [4–9]. Headache is the most frequent complaint and occurs in 15–30% of patients. This problem is usually minor and either resolves spontaneously or is treated with a mild analgesic such as acetaminophen. Gastrointestinal side-effects include diarrhoea, constipation, and elevation of liver transaminases. The elevation of liver enzymes usually is not clinically significant, and may in many cases be secondary to chemotherapy. The selective serotonin antagonists have anti-arrhythmic properties and several agents have been demonstrated to prolong the QT_c and other EKG intervals [10]. To date, no clinical cardiac abnormalities secondary to the 5-HT_3 antagonists have emerged.

Corticosteroids continue to be effective, convenient, and inexpensive anti-emetics that are useful against nearly all chemotherapy-related emesis. This class of agents is useful in both delayed and acute emesis, with chemotherapy of mild, moderate, and severe emetic potential. Corticosteroids are active parenterally and orally. Although the mechanism of action is not defined, it differs from that of other anti-emetics. Corticosteroids often are sufficient as single agents when the likelihood of vomiting is low. Corticosteroids enhance the activity of other active anti-emetics and are easy to use in combination anti-emetic regimens for moderate or severe emesis [11, 12].

Anti-emetic regimens combining a single dose of dexamethasone with either a serotonin antagonist or metoclopramide are more effective than single-agent therapy. This has been demonstrated in at least a dozen studies, using several anti-emetics in combination, and for emesis induced by cisplatin and other chemotherapeutic agents [11–15]. Typically, anti-emetic efficacy in patients receiving cisplatin rises from 40–50% to 80% when dexamethasone is administered in conjunction with a 5-HT_3 antagonist or metoclopramide [10–16].

Table 2. Single-dose and combination anti-emetic regimens for use in conjunction with chemotherapy associated with a moderate or severe risk of emesis†* [7, 12, 13, 15, 19–27]

Agent	Intravenous Dose	Oral Dose
Dexamethasone	20 mg	20 mg
	Plus one of the following:	
Dolasetron	1.8 mg/kg	200 mg
Granisetron	10 μg/kg	1 mg
Ondansetron	8 mg or 0.15 mg/kg	16 mg
Tropisetron	5 mg	5 mg

*Time of administration for all agents is immediately before chemotherapy; †Side-effects include headache, elevation of liver enzymes, and constipation.

With moderately emetogenic agents such as cyclophosphamide, carboplatin, or anthracyclines, the rate of complete control rises to over 90% when a 5-HT_3 antagonist is administered in combination with dexamethasone [12]. Recommended combination corticosteroid 5-HT_3 regimens are listed in Table 2.

Dexamethasone is the most frequently used corticosteroid, although other agents in this class may be as effective. Typically, doses of dexamethasone used for anti-emetic control, as part of a combination regimen, are in the range of 8–20 mg, administered intravenously (i.v.) or orally. When given as a single agent for mild emesis, the dose is often as low as 4 mg, administered orally. Side-effects with dexamethasone at these doses are generally mild.

Older anti-emetic agents

In the past, many agents have been used to treat chemotherapy-induced emesis. These drugs are less effective and have more adverse effects than the selective 5-HT_3 antagonists, metoclopramide, and corticosteroids. Despite their lower therapeutic index, these agents are worth discussing because of their secondary or tertiary roles in controlling chemotherapy-induced emesis and to provide an accurate historical perspective.

Lorazepam, a benzodiazepine, has only modest anti-emetic effects, but because of its anxiolytic and amnestic properties, it is accepted well by patients. It also is effective in reducing akathisia and is useful in lessening dystonic reactions secondary to phenothiazines. The major side-effect of lorazepam is sedation. Today, lorazepam is recommended as an adjunct to effective anti-emetics; it is not recommended as a single agent [16]. It may have a useful first-line role in patients with anticipatory or conditioned emesis, which is discussed below.

The phenothiazines, such as prochlorperazine, are commonly used in general medicine for the control of emesis, although their efficacy and low therapeutic index have been questioned [1]. Phenothiazines that are administered in high intravenous doses are more efficacious than the members of this class that are given orally or intramuscularly. Orthostatic hypotension is a frequent and occasionally dangerous adverse effect that is not found with other frequently used anti-emetic agents. Other side-effects of the phenothiazines include sedation and dystonic effects.

The activity of cannabinoids such as dronabinol (delta-9-tetrahydrocannabinol) as anti-emetics is similar to that of the oral phenothiazines, but it is markedly lower than that of metoclopramide, 5-HT_3 antagonists, or corticosteroids [1, 17, 18]. Side-effects are more common than with the phenothiazines or other anti-emetics, and include sedation, dizziness, ataxia, orthostatic hypotension, dry mouth, and dysphoria [1, 17]. Although cannabinoids have limited anti-emetic properties, their role in anti-emetic therapy has not been well defined, especially with the availability of other more effective and less toxic agents. In a randomised, double-blind, cross-over study that compared oral tetrahydrocannabinol (THC) with inhaled marijuana, both agents had similar, but low activity [18]. There was a trend towards patient preference for the THC capsules [18].

Anti-emetic dosing schedules

The ideal dosage for the serotonin antagonists remains controversial. The most practical and cost-effective approach for using these agents in any setting is a single-dose regimen. Since these drugs are not schedule-dependent, single-dose regimens beginning immediately before the administration of cisplatin are very effective. There is no evidence that multiple-dose regimens are superior to the more convenient and less expensive single-dose alternative.

Results of most reported studies indicate that single doses of granisetron in the 1 mg oral dose (10 μg/kg i.v. dose) range and of ondansetron in the 8–0.15 mg/kg (i.v. dose) range are more effective than lower doses and as effective as higher doses [5, 8, 9, 19–21]. In the majority of studies, granisetron at 10 μg/kg was as effective as granisetron 40 or 160 μg/kg; ondansetron at 8 or 0.15 mg/kg was as effective as ondansetron 32 mg [5, 19–21]. The dosing of dolasetron is probably the most carefully analysed of any of the 5-HT_3 anti-emetic agents. Trials involving more than 1300 patients have shown that the most effective dose is 1.8 mg/kg, and that both higher and lower doses produce inferior results [6, 7, 23–27]. In addition to the above dose, a single oral dolasetron dose of 200 mg is recommended. Although tropisetron dosing is less thoroughly tested, studies have indicated that a single dose of 5 mg gives results similar to those of the other agents at their most effective doses [28]. These doses and regimens are outlined in Table 2.

DELAYED AND ANTICIPATORY EMESIS

Delayed and anticipatory (or conditioned) emesis are significant problems that require prophylactic treatment when the clinical situation indicates risk. Delayed emesis is often defined as emesis that begins 24 h after the administration of chemotherapy [29]. The potential for chemotherapeutic agents to cause delayed emesis is commensurate with their propensity to cause acute emesis. If patients receive anti-emetics for acute but not for delayed emesis, the incidence of delayed emesis is 60–80% in patients treated with cisplatin and 20–30% in those receiving carboplatin, cyclophosphamide, or doxorubicin [4, 12, 13, 29–32].

Treatment of delayed and anticipatory emesis differs from the approach to acute emesis. The agents used most often to treat delayed emesis are the corticosteroids. Adding oral metoclopramide enhances this activity [29], but controversy continues about whether the 5-HT_3 antagonists are useful or indicated in delayed emesis [4, 12, 30, 33–36]. In some recent clinical trials with encouraging results, combination anti-emetics for delayed emesis were started at 16 h after chemotherapy, rather than at 24 h [36]. The rationale for this approach was that delayed emesis begins in the 17–24 h

period; control of acute emesis is no longer effective at that point [4].

Conditioned or anticipatory emesis results from poor control of acute or delayed emesis. It is typically associated with anxiety prior to the next dose of chemotherapy, followed by nausea or vomiting before, during, or possibly after the administration of chemotherapy. Prevention of this problem using the most effective anti-emetics with each course of chemotherapy remains the best approach, but treatment of the emesis also can be helpful if it occurs.

Behavioural therapy techniques including desensitisation may be useful in preventing anticipatory emesis [37]. The utility of anxiolytic agents has not been well studied in this setting. However, several anecdotal reports indicate that the benzodiazepines, such as lorazepam, are helpful in preventing emesis when they are given orally over one or several days before the administration of chemotherapy, and on the day of treatment.

MAKING ANTI-EMESIS CONVENIENT, FLEXIBLE, AND ECONOMICAL

With the demonstrated effectiveness of single-dosing regimens and oral combinations of anti-emetic agents, several more convenient and less expensive treatment regimens are now available. These regimens, given immediately before chemotherapy, are well accepted by patients and are convenient to administer by the treating staff.

A recent phase II study demonstrated encouraging results with an all-oral, single-dose combination regimen in 61 patients receiving cisplatin at high doses ($\geq 100\,mg/m^2$) or moderate doses ($\geq 60\,mg/m^2$). Patients were given oral dexamethasone 20 mg plus oral granisetron at either 1 mg (with moderate-dose cisplatin) or 1.5 mg (with high dose cisplatin). Eighty-five per cent of patients had no emesis in the acute period [38]. Additionally, more than 70% of patients had complete control of delayed emesis with a regimen beginning 16 h after cisplatin, as discussed above [36]. The effectiveness of lower doses of anti-emetics, which are associated with decreased drug administration time for nurses and decreased drug preparation time for pharmacists, suggests that substantial cost savings may be realised.

CONCLUSIONS AND FUTURE DIRECTIONS

Advances in anti-emetic therapy have had great impact in clinical oncology. Because of the reduction in emesis with the use of newer agents and combination regimens, nearly all chemotherapy can now be given on an outpatient basis. This allows patients and families to maintain more normal lifestyles. Studies have shown that ambulatory chemotherapy, as opposed to inpatient treatment, is associated with less family burden, equal or greater patient satisfaction, equivalent safety and efficacy, and significant cost savings [39]. Current anti-emetic therapy can be given conveniently by staff, and poses little burden to patients.

Is control of chemotherapy-induced emesis optimal at present? It is likely that the standard of care, the combination of serotonin antagonists and corticosteroids, has achieved the highest degree of effectiveness. Different doses, schedules, or routes of administration of the currently used agents are unlikely to lead to marked improvements. New agents that are selective for 5-HT_3 receptors will probably not yield greater anti-emetic control, because currently available drugs appear to saturate those receptors.

There are two paths to better control of chemotherapy-induced emesis. The first is consistent use of the best techniques that are now available. We know when to employ these agents and how to administer them for the greatest efficacy and convenience of use. Additionally, if healthcare professionals administer these agents in the most economical ways, which do not compromise efficacy, their use will be cost-effective and will allow administration in more settings.

The second path involves increased basic investigation into the neuropharmacology of emesis. At present, it is clear that many different pathways can have an effect on emesis. Agents that block dopamine, serotonin, and pain receptors, as well as the corticosteroids, can be active anti-emetics. Current research investigating the role of agents that block the NK-1 receptor (testing the hypothesis that substance P may be involved in emesis) is ongoing. If this approach is effective, it may also lead to improvements in other cancer-related causes of emesis. Investigation of other potentially important pathways also should be pursued.

Progress in anti-emetic therapy has been accomplished through complementary work conducted in several nations. The enhanced control of chemotherapy-induced emesis provides a model demonstrating that thoughtful research in supportive care can result in major improvements in cancer treatment affecting nearly all patients.

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