LEADING ARTICLE

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Antiemetics for Cancer Chemotherapy–Induced Nausea and Vomiting

A Review of Agents in Development

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Abstract

Significant progress has been made in recent years in developing more effective means of preventing nausea and vomiting induced by cancer chemotherapy. With appropriate application of currently available antiemetic regimens, the majority of patients with cancer who are receiving chemotherapy can anticipate experiencing no emesis during their treatment. Nevertheless, incompletely controlled emesis remains a problem for a significant percentage of patients. Persistent challenges include delayed emesis and emesis following high-dose chemotherapy regimens. The goal of complete prevention of emesis in all patients remains elusive. Therefore, there is a strong rationale for investigating new antiemetic approaches.

New antiemetic agents currently under development target the neurotransmitters serotonin (5-hydroxytryptamine; 5-HT) and substance P. A number of new selective antagonists of serotonin 5-HT_3 receptors are in clinical trials. Given the lack of clinically significant differences between the available 5-HT_3 receptor antagonists, it appears unlikely that any of these new agents will have substantial advantages over currently approved agents. Several other serotonin receptors have been targeted including the 5-HT_4, 5-HT_{1A} and 5-HT_{2A} receptors. Of these approaches, only agonism of the 5-HT_{1A} receptor has produced an agent that has proceeded into clinical testing.

The most exciting new class of antiemetics currently under development focuses on antagonism of the effects of the neurotransmitter substance P. Results of early clinical trials with tachykinin neurokinin NK_1 receptor antagonists demonstrate enhanced control of acute emesis with their addition to currently available agents and promising activity in controlling delayed emesis. Available evidence would strongly suggest that this class of agents will represent the next important advance in efforts to control nausea and vomiting induced by chemotherapy.

From a patient's perspective, chemotherapy-induced nausea and emesis (vomiting and/or retching) are among the most troublesome adverse effects of cancer treatment. Substantial progress has been made over the last decade in developing more effective and better tolerated antiemetic treatments.[1] Nevertheless, chemotherapy-induced nausea and vomiting remain problems for a significant number of patients. Persistent challenges include delayed emesis, particularly following cisplatin, and emesis

following multicycle chemotherapy and high-dose chemotherapy.[2-8]

Effort to prevent chemotherapy induced nausea and emesis have primarily been directed at blocking neurotransmitter receptors involved in the emetic reflex, located predominately in the brain stem and the small intestine. Initially, the dopamine D_2 receptor was the main receptor of interest, given the demonstrated antiemetic activity of a number of dopaminergic receptor antagonists such as the phenothiazines, butyrophenones and metoclopramide.[9,10] The next major breakthrough occurred with the introduction of selective antagonists of the serotonin 5-HT_3 receptor, such as ondansetron and granisetron. These drugs work primarily by antagonism of serotonin binding to 5-HT_3 receptors located on vagal afferent fibres within the gastrointestinal system.[11-14]

An additional class of antiemetics whose mechanism of action remains incompletely elucidated is the corticosteroids. Although a variety of corticosteroids have been employed in clinical trials, dexamethasone has been the most extensively evaluated and is used to the greatest extent in clinical practice.

Another important therapeutic advance in this area has been the recognition of the value of combination antiemetic therapy. Corticosteroids add to the antiemetic efficacy of metoclopramide,[15,16] and the efficacy of selective serotonin receptor antagonists is increased by the addition of corticosteroids[17-22] and dopamine receptor antagonists.[23-25]

At present, the combination of a selective 5-HT_3 receptor antagonist and a corticosteroid represents the antiemetic regimen of choice in patients receiving chemotherapy with moderate to high emetogenic potential.[26] This combination completely prevents acute emesis in 70 to 80% and 60 to 70% of patients receiving moderately and highly emetogenic chemotherapy, respectively.[19,20,22] However, the serotonin receptor antagonists are not as effective in preventing delayed emesis, particularly following cisplatin.[27,28] Currently, corticosteroids combined with dopaminergic receptor antagonists or 5-HT_3 receptor antagonists are the treatment of choice in this setting. Even with the best available therapy, however, approximately 50% of patients will still develop delayed emesis following cisplatin.[3,29] Therefore, there remains a need to develop more effective antiemetic therapeutic approaches, particularly in the setting of delayed emesis and emesis following high-dose chemotherapy. In this article, the status of a number of new antiemetic agents under development is reviewed. We focus on agents which target the neurotransmitters serotonin and substance P.

1. Compounds that Target Serotonin Receptors

1.1 Serotonin 5-HT_3 Receptor Antagonists

The development of 5-HT_3 receptor antagonists as antiemetic agents represented a major advance in controlling chemotherapy-induced nausea and vomiting. These drugs appear to primarily work by antagonising the binding of serotonin (released from the enterochrommafin cells in the wall of the gastrointestinal tract following chemotherapy) to 5-HT_3 receptors on vagal and splanchnic afferent fibres (also located in the wall of the gastrointestinal tract). Stimulation of the latter receptors leads to an increase in afferent input to areas in the hindbrain which control the emetic reflex.[30]

A number of 5-HT_3 receptor antagonists are now available in oral and intravenous formulations for clinical use, including azasetron, dolasetron, granisetron, ondansetron, ramosetron and tropisetron. Although these agents have several preclinical differences, they all seem to have comparable clinical efficacy and minimal adverse effects.[11,12]

Despite the lack of meaningful clinical differences between the available 5-HT_3 receptor antagonists, a limited number of efforts are being made to develop additional agents in this class. Compounds in varying stages of development include itasetron, lerisetron, palonosetron and N 3389.[31-34] Itasetron and N 3389, in addition to their activity as 5-HT_3 receptor antagonists, also function as antagonists of the 5-HT_4 receptor.[34,35] The putative advantages of these new agents compared with approved 5-HT_3 receptor antagonists relate to increased affinity for

the 5-HT_3 receptor, enhanced bioavailability or prolonged half-life. Given the appreciable differences that already exist with respect to these factors with approved 5-HT_3 receptor antagonists, it seems doubtful that any of these new agents will prove to be superior to existing ones.

1.2 Agonists of Other Serotonin Receptors

Other serotonin receptors are being evaluated as potential therapeutic targets. 5-HT_{1A}, 5-HT_{2A} and possibly 5-HT_4 receptors are involved in the genesis of emesis.[36] A number of compounds that have agonistic activity at these receptors have been developed.

In preclinical models, the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT) was shown to block emesis induced by a wide variety of stimuli, such as motion, xylazine and cisplatin in the cat.[37] Likewise, in the *Suncus murinus*, vomiting induced by a wide spectrum of stimuli such as nicotine, veratrine, cisplatin, copper sulphate and motion was blocked by 5-HT_{1A} receptor agonists.[38] LY 228729, a well characterised 5-HT_{1A} receptor agonist, showed activity against motion-induced emesis in the cat,[39] and against conditioned-emesis and emesis induced by ditolyguanidine, cisplatin, ipecac (ipecacuanha), emetine and the 5-HT_3 receptor agonist m-(chlorophenyl)-biguanide in the pigeon.[40,41] There was also an indication that LY 228729 may be more efficacious than 5-HT_3 receptor antagonists in controlling emesis in these settings.[41] Despite these encouraging results, clinical studies with these agents have yet to be reported. A small comparative trial of ondansetron and the 5-HT_{1A} agonist buspirone in patients receiving cisplatin, showed superior antiemetic activity for ondansetron.[42]

Agonists of the 5-HT_{2A}/5-HT_{2C} receptor have also shown potential value as antiemetics in preclinical systems. DO1 (+/–)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, a centrally acting 5-HT_{2A}/5-HT_{2C} receptor agonist, dose-dependently blocked the emesis induced by motion and cisplatin in *Suncus murinus*.[43]

The 5-HT_4 receptor has also been viewed as a possible target for antiemetic drug development. 5-HT_4 receptor agonists might theoretically be of value via 2 possible mechanisms: (i) inhibition of serotonin release from enterochromaffin cells; and (ii) restoration of caudally driven peristaltic waves in the upper gastrointestinal tract. A number of agents with mixed 5-HT_4 agonist/5-HT_3 antagonist activity have been evaluated in preclinical models.[44] Despite the theoretical promise, to data limited clinical experience with these agents suggests a modest role in controlling chemotherapy-induced emesis.[45]

There is a strong preclinical rationale for agents that act at serotonin receptors other than the 5-HT_3 receptor as antiemetics and further testing is warranted. A 5-HT_{1A} receptor agonist is now entering phase I testing and further development of such compounds is awaited with interest.

2. Tachykinin Neurokinin NK_1 Receptor Antagonists

The most exciting new class of antiemetic agents currently under development is that which antagonises the effects of the neurotransmitter substance P. Substance P is an 11–amino-acid neuropeptide of the tachykinin family of peptides, originally named for their vasorelaxant properties.[46,47] Substance P is found in the gut and CNS and is released in response to noxious stimuli such as pain. It can mediate a number of vegetative responses including emesis. When injected into ferrets, the animal model employed to demonstrate the therapeutic efficacy of the 5-HT_3 receptor antagonists, substance P can induce emesis.[48,49]

Substance P exerts its effects by binding to a specific neuroreceptor, the tachykinin neurokinin NK_1 receptor. A number of peptide compounds that selectively block the NK_1 receptor have been identified.[48,50-54] A unique feature of NK_1 receptor antagonists, not shared by the 5-HT_3 receptor antagonists or dopaminergic receptor antagonists, is their broad spectrum of antiemetic activity in preclinical models. The NK_1 receptor antagonist CP 99994 has been shown to prevent emesis induced by a wide

range of emetic stimuli, such as apomorphine, morphine, nicotine, copper sulphate, ipecac, radiation, cyclophosphamide, cisplatin, motion and anaesthesia in the ferret, dog, cat and *Suncus murinus*.[55-60]

Another interesting observation with this class of agents relates to their apparent site of action. Unlike the 5-HT_3 receptor antagonists which appear to primarily work at a peripheral site, the NK_1 receptor antagonists require entry into the CNS to demonstrate an antiemetic effect. The quaternised NK_1 receptor antagonist L 743310, which poorly penetrates the blood-brain barrier, was ineffective against cisplatin-induced emesis when injected systemically into ferrets. The same compound demonstrated comparable efficacy to L 741671, an NK_1 receptor antagonist that penetrates the brain, when it was injected centrally in the vicinity of the nucleus tractus solitarius.[50]

A third preclinical finding which has significantly enhanced interest in this class of agents is the observation that they work not only in animal models of acute emesis but also in recently elucidated delayed emesis models. The NK_1 receptor antagonists CP 99994 and GR 205171 showed activity in cisplatin-induced acute and delayed emesis in ferrets and piglets, respectively.[51-61]

Given the unique features demonstrated by this class of agents in preclinical studies, there has been considerable anticipation of the first results of clinical trials of their use as antiemetics in humans. Over the past 2 years, results of the initial studies evaluating this class of agents for chemotherapy-induced emesis have begun to appear.

Kris et al.[62] reported the first clinical experience with an NK_1 receptor antagonist in cancer patients. In a small, dose-ranging, open-label trial of CP 122721 added to a regimen of 5-HT_3 receptor antagonist and dexamethasone, they observed an improvement in the control of delayed emesis from 17% without CP 122721 to 83% with the addition of a single dose of CP 122721 before cisplatin. When compared with ondansetron, another NK_1 receptor antagonist, L 758298, was shown in a double-blind, randomised study in patients who were cisplatin-naive to be almost equal in efficacy when used alone to ondansetron alone in acute emesis but superior in the delayed phase.[63]

Two other NK_1 receptor antagonists were tested in separate multicentre, double-blind, placebo-controlled trials; CJ 11974 and MK 869 were found to be significantly superior to placebo in controlling cisplatin-induced delayed emesis (table I).[64,65] In the trial of MK 869, there was a nonsignificant improvement in the control of delayed emesis when the drug was given before cisplatin and twice daily on days 2 through 5 after cisplatin as compared with its administration as a single dose prior to cisplatin. Both compounds also improved the prevention of acute emesis when combined with granisetron and dexamethasone, although this effect was only significant with MK 869. Both agents were well tolerated, with no clear-cut significant drug-related toxicity noted. Similar results were obtained more

Table I. Randomised trials evaluating the efficacy of tachykinin neurokinin NK_1 receptor antagonists in acute and delayed cisplatin-induced emesis

Reference	Regimen		n	Antiemetic outcome (% of patients with no emesis)	
	acute (day 1)	delayed (days 2-5)		acute (day 1)	delayed (days 2-5)
Hesketh et al.[64]	Granisetron + dexamethasone + placebo	Placebo	31	66.7	36.6
	Granisetron + dexamethasone + CJ 11974	CJ 11974	30	85.7	67.8*
Navari et al.[65]	Granisetron + dexamethasone + placebo	Placebo	51	57	33
	Granisetron + dexamethasone + MK 869	MK 869	54	77 †	82 ‡
	Granisetron + dexamethasone + MK 869	Placebo	54	83 †	78 ‡

* $p<0.05$ *vs* placebo; † $p<0.01$ *vs* placebo (acute); ‡ $p<0.001$ *vs* placebo (delayed).

recently in a double-blind, randomised, parallel group study that also evaluated MK 869 and L 758298 (the prodrug of MK 869) for the prevention of cisplatin-induced emesis in patients who were cisplatin-naive.[66] In this trial, L 758298 combined with dexamethasone given before cisplatin was significantly inferior to ondansetron plus dexamethasone in the prevention of cisplatin-induced acute emesis; however, as in prior trials, delayed emesis was better controlled in the arm receiving MK 869 following cisplatin.

3. Conclusion

Despite the significant progress made over the past 15 years in the development of more effective and better tolerated means to prevent chemotherapy-induced nausea and vomiting, a significant number of patients still experience nausea and emesis, especially when treated with highly emetogenic chemotherapy regimens. Efforts continue to identify more effective antiemetic agents. Current studies focus on additional 5-HT_3 receptor antagonists, 5-HT_{1A} receptor agonists and NK_1 receptor antagonists. Of these, the latter agents appear to have the most potential to further enhance antiemetic control.

The NK_1 receptor antagonists are well tolerated and not associated with unusual or severe toxicity.[62-67] The limited data available on this class of agents demonstrate that as single agents they are no better than 5-HT_3 receptor antagonists in preventing cisplatin-induced acute emesis and when combined with dexamethasone may be inferior to the combination of 5-HT_3 receptor antagonists and dexamethasone in the acute setting, although when combined with 5-HT_3 receptor antagonists and dexamethasone they seem to enhance the control of acute emesis compared with 5-HT_3 receptor antagonists and dexamethasone alone. However, the most interesting aspect of NK_1 receptor antagonists is the evidence that when given prior to cisplatin, whether combined with 5-HT_3 receptor antagonists and dexamethasone or with dexamethasone alone, they are superior to placebo for the control of cisplatin-induced delayed emesis.[64,65]

The available data on the NK_1 receptor antagonists are still preliminary and exploratory in nature. Future studies are needed to address a number of critical issues, including: (i) confirmation that the addition of an NK_1 receptor antagonist to a 5-HT_3 receptor antagonist and dexamethasone significantly improves the control of acute emesis; (ii) assessment of the value of NK_1 receptor antagonists for cisplatin-induced delayed emesis as single agents and in combination with conventional agents such as dexamethasone and metoclopramide; (iii) the most appropriate schedule and timing that will optimise the control of acute and delayed emesis; and (iv) evaluation of NK_1 receptor antagonists with non-cisplatin chemotherapy, especially in the high-dose chemotherapy setting. The completion of well designed trials are necessary to address these issues and provide enough information to define the true utility and place of NK_1 receptor antagonists in the management of chemotherapy-induced nausea and emesis.

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