

REVIEW ARTICLES

Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting

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Despite major advances, emesis remains a major problem in the context of cancer chemotherapy and in the postoperative period. A better understanding of the relevant neurocircuitry, especially the central pattern generator responsible for emesis and the central role of substance P, led to the development of a new class of antiemetics: the neurokinin-1 (NK1) receptor antagonists. Aprepitant is the first NK1 receptor antagonist approved for use in postoperative nausea and vomiting, but several other compounds are currently being investigated for their potential as antiemetics in the postoperative and cancer chemotherapy settings.

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Nausea and vomiting

Nausea is an unpleasant sensation that refers to an inclination to vomit. Retching is an involuntary effort to vomit that does not result in ejection of gastric contents. Vomiting is the forceful expulsion of gastrointestinal contents from the stomach through the mouth. Motor changes during vomiting involve both respiratory and gastrointestinal muscles. Before expulsion of the gastric contents, the glottis is closed, the diaphragm and the muscles of the abdominal wall contract whereas the oesophagus contracts longitudinally and the gastro-oesophageal sphincter zone relaxes. This results in the expulsion of the gastric contents that is facilitated by a retrograde contraction of the cervical oesophagus and a relaxation of the portion of the diaphragm that surrounds the oesophagus. This motor act is coordinated by brainstem structures.

Primarily recognized as a protective reflex occurring in response to the ingestion of hazardous compounds (emesis was used as a therapeutic tool in ancient civilizations),⁸ vomiting is in fact a distressing symptom and a particularly unpleasant side-effect associated with various medical interventions.¹⁵ Emesis remains a critical problem during recovery from surgical procedures, particularly in the ambulatory setting, in anticancer cytotoxic therapy, and in circumstances involving motion and vestibular disturbances (e.g. Ménière's disease). Vomiting can also occur in natural circumstances where its benefits remain obscure (e.g. pregnancy sickness).

Postoperative nausea and vomiting

Every year, more than 100 000 000 patients are anaesthetized throughout the world. Nausea and vomiting are two of the most common and distressing symptoms that can follow procedures requiring anaesthesia.^{54 59} Attempts to quantify the distress caused by postoperative nausea and vomiting (PONV) have led to North American and German or Turkish patients declaring that they would be prepared to spend up to 100 US\$ (75€ or £70) to avoid them.^{29 45} Although PONV is usually self-limiting and not lethal, it can lead to significant clinical problems. They include increased postoperative pain, dehydration, electrolyte imbalance, dehiscence of surgical wounds, haemorrhage, oesophageal rupture, and aspiration pneumonia, the most severe complications being rare. In addition, PONV imposes an economic burden by extending recovery room stay, delaying discharge from hospital, and increasing unanticipated admissions of surgical outpatients.^{28 33}

PONV has been associated with the use of general anaesthetics since the introduction of general anaesthesia.¹ In the chloroform and ether era, the incidence of PONV was as high as 80%. Despite improvements in the prevention of PONV and development of new drugs, the current

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overall incidence of PONV is estimated to be ~30%.²⁶ This incidence can reach 70% in groups of high-risk patients.^{6 30 61} Up to 21% of patients will experience nausea and vomiting in the recovery room, for which they will receive antiemetic drugs.^{44 47 65} In studies that distinguish between nausea and vomiting, the incidence of nausea ranges from 38% to 52% and that of vomiting from 21% to 33% during the first 24 postoperative hours.^{3-5 21 48} When the study period is extended to 72 h, the incidence of nausea ranges from 10% to 72% and that of vomiting from 10% to 17%.^{12 66} Many methodological differences may explain such large ranges. Although nausea and vomiting have been for long considered as steps of the same process, some data suggest that the pathophysiology of the two events may differ. Indeed, risk factors for PONV are different.^{22 66}

Neurocircuitry involved in emesis

Vomiting may be triggered by various inputs or a combination of inputs. Considering PONV, enterochromaffin cells in the stomach and intestine release serotonin. Serotonin binds to 5-hydroxytryptamine type 3 (5-HT₃) receptors in the gastrointestinal tract. This binding results in stimulation of vagal afferents in the gastrointestinal tract that conduct impulses reaching brainstem structures located between the levels of the obex and the nucleus ambiguus, such as the area postrema. Located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle, the area postrema has a critical role in the central mechanism of vomiting. In addition to receiving vagal inputs, this highly vascularized structure can detect emetic agents in the blood and in the cerebrospinal fluid as it lacks a blood–brain barrier. Therefore, the area postrema is considered as a chemoreceptor trigger zone. The area postrema has neurones that project to the medial part of the nucleus tractus solitarius, the subnucleus gelatinosus. The nucleus tractus solitarius also receives inputs from the vagus nerve and from the enterochromaffin, the vestibular, and the limbic system. From the nucleus tractus solitarius, efferent neurones reach the rostral nucleus, the nucleus ambiguus, the ventral respiratory group, and the dorsal motor nucleus of the vagus. It has been proposed that these latter structures are driven by an ‘afferent relay station’ that integrates the outputs from the neurones in the nucleus tractus solitarius.

Thus, the central structures involved in the pathophysiology of vomiting are disseminated throughout the medulla oblongata of the brainstem,³⁴ making it inappropriate to group them in a precise anatomical entity as a ‘vomiting centre’.^{24 42} The structures are scattered in the Bötzing complex (a region of the brainstem also critical for respiratory rhythmogenesis) and are designated as the ‘central pattern generator for vomiting’.

Neurotransmitter receptor systems involved in the mediation of signals leading to nausea and vomiting

include dopaminergic (D₂), cholinergic (muscarinic), histaminergic (H₁) serotonergic (5-HT₃), and neurokinin NK1 systems. The corresponding receptors are potential targets for antiemetic drugs. Even if the numerous neurochemicals involved in the neurocircuitry of emesis may not have been fully identified, the two main inputs to the central pattern generator are from the abdominal vagal afferents via the nucleus tractus solitarius⁴⁶ and from the chemoreceptive trigger zone located in the area postrema.³⁹

Experimental development of the neurokinin-1 (NK1) receptor antagonists

The introduction of selective 5-HT₃ receptor antagonists or serotonin type 3 receptor antagonists has incontestably represented a major advance in the control of acute emesis associated with cytotoxic therapy and surgery. However, further improvement is still needed. An attractive strategy to block emesis, irrespective of its eliciting stimulus, would be to treat patients with a pharmacological agent able to depress the activity of neurones within the medullary emetic circuitry. Chemicals acting as partial (e.g. buspirone and ipsaspirone) or full (e.g. 8-OH-DPAT and SUN 8399) agonists of the 5-HT_{1A} receptor have shown broad-spectrum antiemetic activity in several species without marked adverse effects.⁵³ These compounds were expected to be clinically relevant. Unfortunately, most investigations in various animal models have shown that 5-HT_{1A} receptor agonists usually exhibit weak antiemetic properties against cisplatin-induced emesis; therefore, their clinical development was not considered pertinent at that time. Thus, the pharmacological quest to make available a highly effective broad-spectrum antiemetic has led neuroscientists to investigate the role of neurotransmitter systems other than the serotonergic system.

Special attention has been focused on the role of tachykinins since they have been immunohistologically identified in the dorsal vagal complex of the ferret, an area regarded as essential in the elicitation of vomiting. The emetic action of the tachykinin, substance P, was reported by Carpenter and colleagues⁹ in 1984. Its role within the medullary emetic circuitry was demonstrated by Andrews and Bhandari² in 1993 using resiniferatoxin, an ultra-potent capsaicin analogue that exhibits antiemetic properties in the ferret against both centrally and peripherally acting emetic agents. Andrews and Bhandari suggested that resiniferatoxin exerts its antiemetic activity by depleting substance P at a central site in the emetic pathway. Upon these results, potent and highly selective non-peptide NK1 receptor antagonists that cross the blood–brain barrier and antagonize the central effects of substance P were developed as tools for investigation of the physiological role of substance P in emesis. Besides emesis, other potential indications foreseen for such compounds included pain, migraine, rheumatoid arthritis, inflammatory bowel disease, asthma, and chronic bronchitis.

Tachykinins are members of a family of neuropeptides able to rapidly promote a contractile action in smooth muscles and sharing the common C-terminal sequence Phe-Xaa-Gly-Leu-MetNH₂. These compounds include substance P (for pain) and neurokinins A and B (NKA and NKB). They exert their biological activity through three G-protein-coupled receptor subtypes, identified as NK1, NK2, and NK3 receptors.⁵⁵ According to the Montreal nomenclature,³⁷ the NK1 receptor is defined as the mediator of the biological activity encoded by the C-terminal sequence of tachykinins, for which substance P is a more potent agonist than NK_A or NK_B. Since substance P is believed to exert a key role within the central emetic circuitry, selective NK1 receptor antagonists were expected to express potent antiemetic activity.

The nucleus tractus solitarius lying ventrally to the area postrema in the so-called subnucleus gelatinosus is a good candidate for the site of action of NK1 receptor antagonists. Extensive substance P-like immunoreactivity has been identified in this region and the tachykinins have been proposed as transmitters in vagal afferents.^{19 20 51} Experimentally, the substance P-induced discharge of action potentials of single nucleus tractus solitarius neurons recorded in slices of ferret brain stem is inhibited by HSP-117, an NK1 receptor antagonist with potent antiemetic activity.⁶³ These results and the data from positron emission tomography studies in rhesus monkeys²³ suggest that NK1 receptor antagonists exert their main antiemetic action by depressing the neural activity of nucleus tractus solitarius neurons, that is, within the central emetic circuitry. A contribution from peripheral sites is also possible as peripheral injection of sendide, a peptide-based NK1 receptor antagonist, is active against cisplatin-induced emesis in the ferret and this is likely to be through a gastrointestinal tract site of action.⁵⁸ The proposed mechanism involves a block of the NK1 receptors located on vagal terminals in the gut decreasing the intensity of the emetic afferent message transmitted to the medullary emetic circuitry. This peripheral effect of NK1 receptor antagonists might be similar to that of the 5-HT₃ receptor antagonists on the serotonergic activation of vagal terminals. This hypothesis remains to be confirmed.

Clinical applications of the NK1 receptor antagonists

In animals and in humans, the numerous transmitters involved in the emetic process accounts for the incomplete efficacy of single-drug therapies for nausea and vomiting of various aetiologies. Maybe due to their central role on a potential, final common pathway, the NK1 receptor antagonists have offered the prospect of a broader spectrum antiemetic activity than the 5HT₃ receptor antagonists, dopamine receptor antagonists, anticholinergic agents, and corticosteroids. As with pain management,⁶⁴ the efficacy

of NK1 receptor antagonists in treatment of nausea and vomiting is optimized by combining it with other antiemetics from different classes.

Data from published clinical studies seem to confirm the usefulness of the NK1 receptor antagonists in man, in two types of indications: cancer-chemotherapy-induced nausea and vomiting (CINV) and PONV. In contrast, the NK1 receptor antagonists were shown to be less effective in motion-induced nausea, either alone or in combination with a 5-HT₃ receptor antagonist.⁶² The investigational NK1 receptor antagonists studied include GR205171 (vofopitant, GlaxoSmithKline), CP-122721 (Pfizer), CJ-11974 (Pfizer), L-754030 (aprepitant, Merck), and its prodrug MK 0517 or L-758298 (fosaprepitant). Numerous other compounds are under investigation, including casopitant (GlaxoSmithKline), maropitant (Pfizer), netupitant (Helsinn Healthcare), rolapitant or SCH 619734 (Schering-Plough), T 2328 (Mitsubishi Tanabe Pharma), and vestipitant (GlaxoSmithKline).

NK1 receptor antagonists in chemotherapy-induced nausea and vomiting

The prevention of CINV remains the main target in the development of new antiemetics. In this setting, the design of several placebo-controlled trials allowed comparison between NK1 receptor antagonist, 5-HT₃ receptor antagonist (usually ondansetron), a combination of a 5-HT₃ receptor antagonist plus dexamethasone, a combination of a NK1 receptor antagonist with either dexamethasone alone or with a 5-HT₃ receptor antagonist plus dexamethasone (three antiemetics).¹⁶ The recent classification of the antineoplastic agents used in chemotherapy into four groups according to their emetogenicity³⁵ and the better comprehension of the different categories of emetic events during CINV allows for better comparisons between older and newer prevention and treatment regimens.

In the study arms where a NK1 receptor antagonist was administered alone, it proved either ineffective (GR205171, 5 or 25 mg i.v.)²⁵ or not superior to ondansetron (L-758298, 60 or 100 mg i.v.),¹¹ in the control of acute CINV after high doses of cisplatin. Except for this setting, the NK1 receptor antagonists have shown dramatic antiemetic activity in cisplatin-treated patients. This is true for the prevention of acute CINV in association with a 5-HT₃ receptor antagonist or with a 5-HT₃ receptor antagonist plus dexamethasone.

For the prevention of delayed CINV, a single prophylactic dose of NK1 receptor antagonist (CP-122721) proved effective in six out of the seven patients (86%), whereas the combination with a 5-HT₃ receptor antagonist and dexamethasone brought about this result in eight out of 10 patients (80%).⁴⁹ The NK1 receptor antagonists alone proved significantly superior to ondansetron alone in the

prevention of vomiting and nausea on days 2–7 after cisplatin administration.³⁵

The first NK1 receptor antagonist to be marketed in the USA and Europe is aprepitant (Emend* Merck) in an oral presentation. Aprepitant administration is part of the 2008 clinical recommendations of the European Society for Medical Oncology for the prophylaxis of CINV.³⁸ Its pharmacokinetics have been described by Majumdar and colleagues.⁵⁶ After an oral dose, aprepitant bioavailability is 60–65%. Absorption is not affected by food and the serum half-life is 4 h. The drug crosses the blood–brain barrier.³⁶ It is metabolized in the liver, primarily by CYP450 3A4 enzymes, and is excreted in both urine and faeces. Aprepitant potentially competes with other drugs for the same metabolic pathway: the clinical implications are minor except for co-administered corticosteroids, the dose of which should be reduced.⁵⁷

Compared with standard therapy (ondansetron plus dexamethasone), oral aprepitant 125 mg before cisplatin followed by aprepitant 80 mg on days 2–5 after the treatment brings better and more sustained protection against CINV over multiple cycles. Comparing the time course of the antiemetic effect of aprepitant with that of ondansetron or granisetron and that of the combination of the NK1 receptor antagonist and a 5HT₃ receptor antagonist, Hesketh and colleagues⁴¹ showed that serotonin may be more influential in acute CINV (8–12 h), whereas substance P plays the major role in delayed symptoms. The same authors showed that addition of aprepitant to a 5HT₃ receptor antagonist plus corticosteroid regimen abolished the effect of female gender on the success rate of CINV prophylaxis.⁴⁰ The i.v. prodrug, fosaprepitant, is converted to aprepitant within about 30 min: 115 mg of fosaprepitant i.v. is equivalent to 125 mg oral aprepitant.⁵⁰

Casopitan (GlaxoSmithKline) is still under evaluation. Phase II and III studies showed that casopitan 90–50 mg i.v./p.o. in combination with ondansetron and dexamethasone reduces CINV in patients receiving moderately, and also highly, emetogenic chemotherapy.⁷ However, the observed improvements seem to be related mainly to vomiting and less to nausea control.

NK1 receptor antagonists in PONV

Early studies

The first clinical study of an NK1 receptor antagonist in the context of PONV was published in 1999. In this controlled randomized trial in the setting of treatment of established PONV after laparoscopic or open hysterectomy, Diemunsch and colleagues¹⁷ showed vofopitant or GR205171 25 mg i.v. as a single agent to be superior to placebo for complete control of nausea and vomiting. This benefit was maintained throughout the entire 24 h study period. The proportion of patients requiring rescue

medication during the 24 h after drug administration was also less after treatment with GR205171 (61% vs 83% after the placebo). Neither difference across groups for pain severity or need for analgesics ($P=0.2$) nor major adverse event was observed in this study.

Comparing CP-122721 200 mg orally with ondansetron 4 mg i.v. and with the combination of the two agents in the prevention of PONV, Gesztesi and colleagues³² found no differences for postoperative nausea scores among the three groups, but a significantly lower incidence of emetic episodes when CP-122721 was part of the prophylactic regimen. The combination of CP-122721 and ondansetron provided no additional benefit. These results were published as an abstract only. The same group published additional data in 2000³¹ showing, in a dose-ranging approach, that oral CP-122721 200 mg was more effective than oral CP-122721 100 mg. In this controlled randomized trial that involved 277 patients presenting for total abdominal hysterectomy, the combination of CP-122721 and ondansetron significantly prolonged the time to the administration of the first rescue antiemetic drug when compared with either drug alone, and prevented the occurrence of emesis in 98% of the patients. Nevertheless, patient satisfaction was no different than after ondansetron 4 mg. There was no significant difference between the morphine requirement in the CP-122721 and placebo groups during the initial 24 h postoperative period. The only clinically significant adverse event attributed to CP-122721 during the 72 h follow-up period was an increased incidence of headache (22% vs 2% in the placebo group; $P<0.05$).

In another study published so far as an abstract only, oral casopitan 50 mg or placebo was given 60 min before anaesthesia along with ondansetron 4 mg i.v. injected before induction, in 570 patients receiving opioids perioperatively. In the casopitan group, the complete response rate (no vomiting and no rescue) was better than in the placebo group (57% vs 43%; $P<0.05$), irrespective of the postoperative opioid used. Conversely, no difference for nausea was found between the groups.¹⁰

Aprepitant in PONV

In a randomized, multicentre, double-blind phase III trial, 922 patients undergoing open abdominal surgery were allocated randomly to receive one of the three antiemetic treatments before the operation: oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg, or matching placebos for the prevention of PONV. All oral medications were given within 3 h of anticipated induction of anaesthesia and i.v. ondansetron or placebo was infused over 2–5 min immediately before induction, according to the approved prescribing information. Complete response was achieved in 64% of patients in the aprepitant 40 mg group (odds ratio of aprepitant to ondansetron, 1.4; lower bound of the one-sided 95% CI, 1.08), 63% in the aprepitant

125 mg group (odds ratio, 1.4; lower bound of the one-sided 95% CI, 1.04), and 55% in the ondansetron group, showing aprepitant (40 or 125 mg) being non-inferior to ondansetron (4 mg) in achieving complete response (i.e. no vomiting and no use of rescue therapy) for 24 h after surgery. Aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 h (percentage of patients with no vomiting 84%, 86%, and 71%, respectively, in the aprepitant 40 mg, aprepitant 125 mg, and ondansetron groups); and at 48 h post-surgery (percentage of patients with no vomiting 82%, 85%, and 66%, respectively, in the aprepitant 40 mg, aprepitant 125 mg, and ondansetron groups); and in reducing nausea severity in the first 48 postoperative hours.¹⁴ The most commonly reported adverse events were pyrexia, constipation, headache, and bradycardia with no differences between the groups. No major adverse effect attributable to aprepitant was observed.

In another study based on a similar design, aprepitant was superior to ondansetron for prevention of vomiting in the first 24 and 48 h, but no significant differences were observed between aprepitant and ondansetron for nausea control, use of rescue antiemetic, or complete response.²⁷ A *post hoc* analysis of the pooled data from these two randomized active-controlled trials was performed on 541 patients in the aprepitant 40 mg group, 532 patients in the aprepitant 125 mg group, and 526 patients in the ondansetron group, in a modified intention-to-treat analysis. This analysis showed that in the 24 h after surgery, aprepitant 40 mg was more effective than ondansetron for all five endpoints evaluated [no significant nausea (56.4% vs 48.1%), no nausea (39.6% vs 33.1%), no vomiting (86.7% vs 72.4%), no nausea and no vomiting (38.3% vs 31.4%), and no nausea, no vomiting, and no use of rescue (37.9% vs 31.2%); $P < 0.035$ for the odds ratio for each comparison] (Fig. 1). Comparisons of prophylactic antiemetics

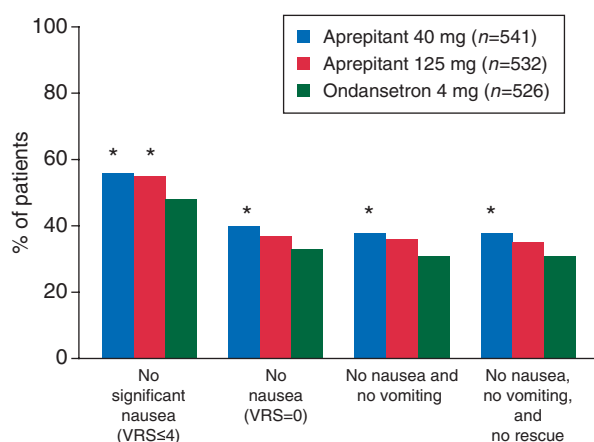


Fig 1 Percentage of patients in the combined modified intent-to-treat population with efficacy endpoints accounting specifically for nausea, by treatment group. VRS, verbal rating scale. *An odds ratio (aprepitant:ondansetron) > 1.0 , $P < 0.05$ in favour of aprepitant (from Diemunsch and colleagues).¹³

should take into account the potential influence of rescue therapy on either nausea or vomiting since once rescue medication is taken, a lack of nausea, vomiting, or both may be due to the prophylactic antiemetic, the rescue therapy, or both. Therefore, the most relevant endpoint of antiemetic prophylaxis is its ability to provide complete protection from vomiting, nausea, and the need for rescue therapy. More patients taking aprepitant achieved this complete protection compared with those taking ondansetron, with the best results seen in the aprepitant 40 mg group. Aprepitant 125 mg tended to show similar or slightly reduced effects compared with aprepitant 40 mg, suggesting a plateau in response and the recommended and approved dose of oral aprepitant for PONV prophylaxis is 40 mg.¹³

Specific advantages of aprepitant in the PONV setting include its oral formulation, easily administered for prophylaxis along with the premedication, the possible use of an i.v. form (fosaprepitant) for treatment of established PONV, the possibility to save the other validated antiemetics as rescue drugs since a change in therapeutic class is recommended in the case of failure of prophylaxis, and possible specific advantages due to the long-lasting effect of this drug. This particular point has been recently documented in the orthopaedic inpatient setting⁶⁷ but may be even more important in the outpatient setting.

Safety

Safety of the NK1 receptor antagonists in man has never been a concern in the clinical studies, and all the investigational drugs were well tolerated, with no drug-related toxicity. No adverse events were reported that would preclude further studies of NK1 receptor antagonists in man. One exception, however, has been a serious episode of dizziness possibly related to oral L-754030 (400 mg). Similarly an increased incidence of mild or moderate headaches was observed after oral CP-122721 (200 mg) in the dose-ranging study. Despite the implication of substance P in pain mechanisms, no obvious effects on pain threshold or on analgesia were observed in the human PONV studies. This is contrary to the results of one study¹⁸ which showed that the NK1 receptor antagonist CP-99994 was effective in pain reduction after third molar extraction.

Other potential indications of the NK1 receptor antagonists include asthma, anxiety, arthritis, migraine, schizophrenia, glaucoma and ocular hypotension, neural injury, and stroke. Recent evidence of prevention of adhesions related to laparoscopic surgery by intraperitoneal administration of aprepitant may be of particular interest.⁵² It is so far unknown, as to whether the doses required to treat CINV and PONV may provoke specific side-effects related to the potential wide-spectrum activity of the NK1 receptor antagonists.

Conclusion

More research is needed to determine the optimal dose of the NK1 receptor antagonists in PONV, the optimal associations with other antiemetics, and the place of these drugs in the prevention, the rescue schemes, or both for PONV and also their use in paediatric patients. Some putative specific benefits bettering terms of superior efficacy for the prevention of nausea and delayed vomiting than other classes of antiemetics represent directions for further work. Also, the possible role of pharmacogenomics in the individual response to the NK1 receptor antagonists in PONV, as observed for the 5-HT₃ receptor antagonists, needs to be explored.^{43 60}

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