REVIEW ARTICLE

Neurokinin-1 Antagonists for Postoperative Nausea and Vomiting

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Abstract

Postoperative nausea and vomiting (PONV) are the second most frequent adverse events after surgery second only to postoperative pain. Despite the advances in antiemetics and implementation of multimodal prophylactic interventions, the clinical management of PONV remains problematic. Neurokinin-1 (NK-1) receptor is a tachykinin receptor found throughout the central and peripheral nervous systems, with a particular affinity towards substance P. NK-1 receptors interact with several parts of the neuronal pathway for nausea and vomiting. This includes the chemoreceptor trigger zone, the gastrointestinal tract, and dorsal motor nucleus of the vagus. NK-1 antagonists are thought to prevent nausea and vomiting by downregulating the emetogenic signals at those points. As more head-to-head trials are conducted between the various anti-emetics, there is emerging evidence that NK-1 antagonists may be more effective in preventing PONV than several other antiemetics currently in use. In this review, we will discuss the pharmacology of NK-1 antagonists, their efficacy in clinical practice, and how they could fit into the framework of PONV management.

Key Points

Neurokinin-1 (NK-1) antagonists appear to be more efficacious than most other antiemetics in preventing postoperative nausea and vomiting (PONV).

NK-1 antagonists are effective when used in combination with other pharmacological PONV prophylaxis.

With the introduction of injectable formulations, NK-1 antagonists may become effective rescue anti-emetic options.

1 Introduction

Postoperative nausea and vomiting (PONV) are common adverse events in the surgical population [1]. It is distressing for patients, increases the risk of postoperative

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complications, and may increase the cost of healthcare [2]. Despite the variety of antiemetics available and a paradigm shift towards universal administration of multimodal antiemetics, PONV remains a significant challenge in postoperative care. Neurokinin-1 (NK-1) antagonists are a newer class of antiemetic demonstrating promising efficacy. In this review, we will discuss the pharmacology and efficacy of NK-1 antagonists, as well as how they could fit into the existing framework of PONV management.

2 PONV in Clinical Practice

While the risk of PONV in the general surgical population is approximately 30% [1], it can be as high as 80% in high-risk patient groups or with high-risk surgical procedures [3]. Patient factors that increase the risk of PONV include female gender, non-smoking status, and personal history of PONV or motion sickness; while perioperative risk factors of PONV include the use of volatile anesthesia, nitrous oxide, opioids, and duration of surgery [1]. Several surgery types are considered high risk, including laparoscopic surgeries, cholecystectomy, pelvic surgeries, thyroid, strabismus repair, and middle-ear surgery [1, 4, 5]. The risk of PONV could also be quantified using risk scores, such as the Apfel score and the Koivuranta score [3, 6], but it should be noted that

neither of these consider the risk associated with the surgical procedure.

Early PONV in the post-anesthesia care unit (PACU) could lead to prolonged stay or unplanned admission in an ambulatory surgical setting. Parra-Sanchez et al. [7] found that the occurrence of PONV prolongs PACU stay by an hour and increases healthcare cost by an average US$74. Late PONV is also associated with increased incidence of unplanned readmission to the hospital [8]. While rare, PONV could also lead to other complications, such as aspiration and suture dehiscence [9].

An updated PONV Consensus Guideline was recently published, which sets out a framework for preoperative risk assessment, implementation of perioperative risk reduction measures, administration of PONV prophylaxis, and rescue treatment when the previous steps are not successful. Notably, the guideline now recommends that patients with any PONV risk factor should receive two PONV prophylactic interventions, and additional prophylactic interventions should be administered in those with more than 2 risk factors [1]. Despite this, the expert panel agreed that there is currently limited evidence on the optimal number or combination of multimodal PONV prophylaxis. Weibel et al. conducted a network meta-analysis and compared the efficacy of over 40 antiemetics in preventing PONV. The authors reported that several antiemetic monotherapies (including prochlorperazine, domperidone, and cyclizine) and combination therapies are not significantly more efficacious than placebo. The efficacy of antiemetic therapies also varies considerably, with NK-1 receptor antagonists, such as aprepitant and fosaprepitant, demonstrating comparable efficacy to dexamethasone–ondansetron and other combination prophylaxis [10]. This indicates that the efficacy of combination therapies is largely dependent on the efficacy of the individual antiemetics and would suggest that risk-stratified antiemetic escalation should also consider the efficacy of the individual anti-emetics.

3 PONV Pathology and Pharmacodynamics of NK1 Inhibitors

Nausea and vomiting, a reflexive process, can be triggered by multiple afferent pathways, including ascending signals from the gastrointestinal tract, the vestibular-cochlear system, and the chemoreceptor trigger zone. The impulses are processed through the vomiting center and lead to a single efferent pathway, which reverses the direction of peristalsis in the stomach and esophagus and leads to the expulsion of the stomach contents [11].

Neurokinin-1 receptor is one of the three neurokinin receptor subtypes and is found in the basal ganglia, brainstem, and throughout the gastrointestinal tract. NK-1 receptor has a particular affinity to substance P, a regulatory peptide released from enterochromaffin cells in response to pain or stress. Activation of the NK-1 receptors by substance P has been shown to activate cholinergic neurons and cause gastrointestinal smooth muscle contraction [12].

The role of substance P in nausea and vomiting was first demonstrated by Carpenter et al. [13], who found that systemic administration of substance P resulted in emesis in dogs. Interestingly, substance P did not induce emesis in animals with the area postrema (later identified as the chemoreceptor trigger zone) surgically ablated [14]. The study was subsequently repeated in ferrets with near identical findings [15]. Carpenter et al. [16] also demonstrated in dogs that administration of substance P to the area postrema resulted in low frequency neuronal discharges. NK-1 receptors were also identified in the area postrema [17]. Together, these experimental findings suggest that NK-1 receptors in area postrema are central to the emetogenic action of substance P.

In addition, NK-1 receptor is also highly expressed in other parts of the neurocircuitry responsible for nausea and vomiting. The solitary tract (NTS) is thought to act as the processing center for the various emetogenic stimuli [18]. NTS is also involved in the emetogenic action of substance P, and stereotactic injection of NK-1 antagonist into the NTS reduces cisplatin-induced vomiting [19], while NK-1 receptor blocking antiemetics have been shown to displace the binding of substance P from the NTS [20]. Another area involved is the dorsal motor nucleus of the vagus (DMV), which reduces the muscle tone of the lower esophageal sphincter and reverses the normal peristaltic direction of the gastrointestinal tract [11]. NK-1 receptors are highly expressed in the DMV [21], and stereotactic microinjection of NK-1 receptor antagonist into the DMV alters gastric motility [22]. Substance P administration in the DMV results in the depolarization of motor neurons innervating the stomach and duodenum [23]. Lastly, NK-1 receptors are also found in abundance in the gastrointestinal tract, where they are thought to regulate smooth muscle contraction and water and ion absorption [24, 25].

Early animal studies suggested that the antiemetic efficacy of NK-1 antagonists depends primarily on its central action. Tattersall et al. [19] compared the efficacy of two NK-1 antagonists with similar receptor affinity, but one had poor blood brain barrier (BBB) permeability owing to its quaternary chemical structure (L-743,310). The authors reported that when administered peripherally, L-743,310 had virtually no antiemetic efficacy despite its receptor affinity. However, when it was administered centrally, L-743,310 was effective in reducing chemotherapy-induced nausea and vomiting. On the other hand, the BBB permeable NK-1 antagonist was effective when given peripherally or centrally. Considering the experimental data linking area postrema to emesis and substance P, area postrema is likely a

key therapeutic target for NK-1 blocking antiemetics. On the other hand, the broad spectrum of NK-1 antagonists in treating emesis due to various central and peripheral stimuli suggests that NK-1 antagonists might affect the 'final common pathway' of emesis, which includes the NTS and DMV [26].

4 Aprepitant

Aprepitant is an NK-1 antagonist first licensed in 2003 for the prevention of chemotherapy-induced nausea and vomiting. In 2007, studies by Diemunsch et al. [27] and Gan et al. [28] both reported that aprepitant prophylaxis was associated with a lower incidence of vomiting than ondansetron, and the Food and Drug Administration (FDA) subsequently approved its use for PONV prophylaxis. The dose recommended for PONV prophylaxis is 40 mg.

Aprepitant is a partially insoluble crystalline solid, with chemical formula $C_{23}H_{21}F_7N_4O_3$ and a molecular weight of 534 g/mol (Fig. 1). As a result of its poor water solubility, it is commercially available in capsules for oral administration. The bioavailability of aprepitant is estimated to be 60–65%. It is extensively protein-bound in the circulation and has an estimated volume of distribution of 70 L after oral administration. Aprepitant is metabolized in the liver by cytochrome p450 (CYP) 3A4, primarily through dealkylation and has several weakly active metabolites. Aprepitant and its metabolites are primarily excreted in the feces with very little renal elimination. The plasma clearance is estimated to be 62–90 mL/min, with a half-life of 9–13 h [29]. However, its duration of action is reported to be more than 40 h [30].

Singh et al. [31] conducted a meta-analysis, which included trials of aprepitant compared to placebo and aprepitant compared to other anti-emetics as a part of multimodal prophylaxis. They concluded that while aprepitant (40, 80, and 125 mg) had significantly lower incidence of vomiting on both postoperative days one and two, the clinical significance of the findings was not clear when considering the heterogeneity in study design. As a single agent prophylaxis, 40 mg aprepitant had similar efficacy as 0.075 mg palonosetron [32]. Clinical trials have reported that aprepitant was more effective in preventing PONV when compared to ondansetron [28, 33].

The use of aprepitant in combination with other pharmacotherapies has also been studied. Ham et al. [34] conducted a clinical trial of high-risk (Apfel scores of 3 or 4) patients who underwent laparoscopic gynecological surgery under sevoflurane anesthesia. Patients were randomized to receiving aprepitant 80 mg or placebo, in addition to ondansetron bolus plus ondansetron-containing patient-controlled analgesia (PCA). Patients who received aprepitant had significantly higher complete response and less nausea in the 24 h after surgery. Several other studies have also shown that aprepitant was efficacious when added to ondansetron for PONV prophylaxis [35–37]. This was also seen when aprepitant was added to ramosetron [38] or dexamethasone [39]. Yoo et al. [40] conducted a clinical trial of female patients with Apfel score of 3 or 4 undergoing major orthopedic procedures or thyroidectomy.
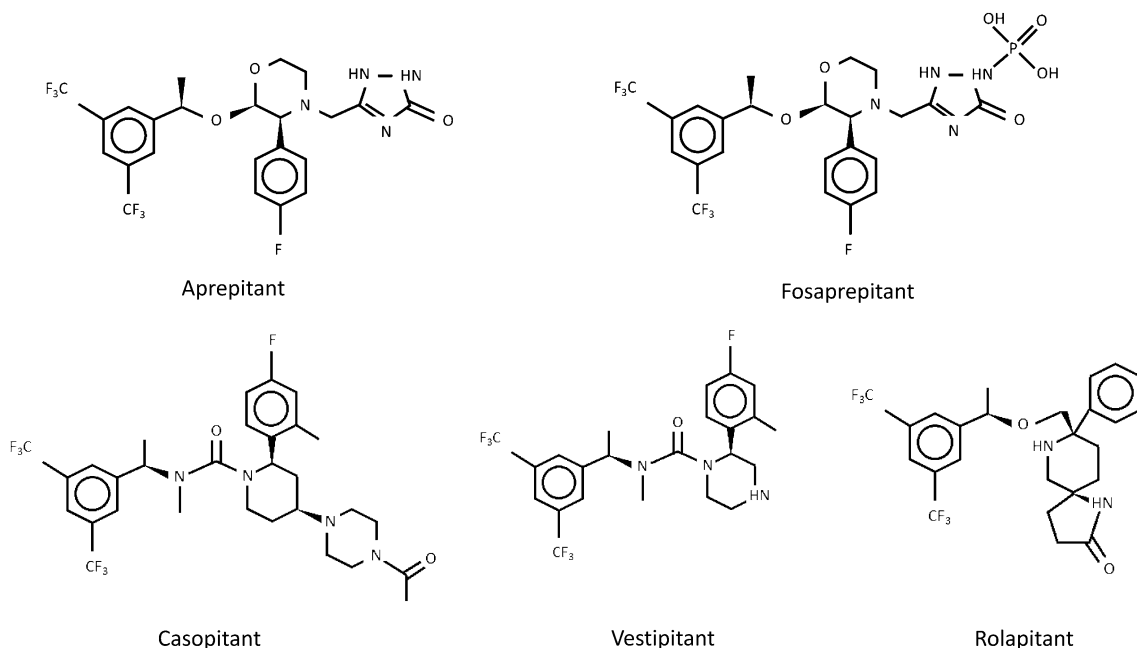

Fig. 1 Chemical structure of NK-1 antagonists

The authors found that 80 mg aprepitant in combination with 0.075 mg palonosetron did not result in lower risk of PONV nor lower rescue antiemetic requirement when compared to palonosetron alone.

The use of aprepitant as a third or fourth prophylactic agent is not well studied. Morais et al. [41] conducted a clinical trial with patients with Apfel scores of 3 or 4 undergoing laparoscopic surgeries. Patients were anesthetized with propofol total intravenous anesthesia (TIVA) and received ondansetron and dexamethasone prophylaxis. They were then randomized to receive either aprepitant 80 mg or placebo. Those who received aprepitant had a significantly lower risk of vomiting in the 24 h after surgery. Aprepitant and scopolamine patch added to ondansetron plus dexamethasone significantly reduced the nausea and vomiting severity after sleeve gastrectomy [42]. Grigio et al. [43] conducted a clinical trial on high-risk patients undergoing mastectomy and found that 80 mg aprepitant added to palonosetron plus dexamethasone did not reduce the risk of PONV. This was consistent with the study by Yoo et al. [40], which reported that 80 mg aprepitant did not further reduce the risk of PONV when used in addition to palonosetron. This further highlights the complexity in optimizing multimodal PONV prophylaxis regimen and requires further targeted studies.

Weibel et al. [10] conducted a network meta-analysis of medications used for PONV prophylaxis. The authors computed direct and indirect comparisons between various single-agent prophylaxes, as well as drug combinations. The authors found that aprepitant monotherapy was more efficacious than ondansetron, palonosetron, droperidol, scopolamine, and haloperidol monotherapies. Aprepitant monotherapy was also non-inferior when compared to most two or three antiemetic combinations. The literature search was last updated in April 2020.

Similar to palonosetron, aprepitant was also shown to be beneficial in ambulatory surgery due to its long duration of action and lower risk of postdischarge nausea and vomiting (PDNV). Vallejo et al. [36] conducted a clinical trial of 150 patients with moderate-to-high risk undergoing ambulatory plastic surgery and found that 40 mg aprepitant plus 4 mg ondansetron was associated with a significantly lower incidence of PDNV than ondansetron alone.

Interestingly, Moon et al. [32] also found that after laparoscopic gynecological surgeries, 40 mg aprepitant prophylaxis was associated with significantly lower opioid requirement from 6 to 24 h postoperatively. Considering the role of substance P in nociception, it is possible that NK-1 antagonists also have anti-nociceptive efficacy.

Given that aprepitant is an oral preparation, its onset is limited by enteral absorption. It was estimated that the time to peak plasma concentration (T_{max}) is approximately 3 h. This makes it unsuitable as a rescue therapy [44].

4.1 Fosaprepitant

Fosaprepitant is a prodrug of aprepitant with an additional phosphonate group (Fig. 1). It is formulated as a dimeglumine salt, available as a powder or solution for injection. It is administered as an intravenous injection, with the manufacturer recommending that a 150 mg dose be administered as a slow infusion over 20–30 min [45].

On intravenous administration, it is rapidly converted to aprepitant by ubiquitous plasma phosphatases [46] with an estimated half-time of 2.3 min [47]. It subsequently undergoes metabolism and clearance in a similar manner to aprepitant, albeit with considerably higher peak concentration [47].

While fosaprepitant was approved only for chemotherapy-induced nausea and vomiting (CINV), several studies assessed the efficacy of fosaprepitant in preventing PONV. Kakuta et al. [48] conducted a clinical trial of low- to medium-risk patients undergoing lower limb surgery and reported that 150 mg fosaprepitant was associated with significantly lower risk of vomiting. Similar findings were also reported in patients at high risk of PONV undergoing craniotomy and gynecological surgeries [49–51]. In patients undergoing craniotomy, 150 mg fosaprepitant and 10 mg dexamethasone were associated with significantly lower risk of PONV when compared to droperidol 1.25 mg and dexamethasone 10 mg [52].

In the network meta-analysis by Weibel et al. [10], fosaprepitant had the largest effect size of all single-agent prophylaxes and was more efficacious than ondansetron + dexamethasone, ondansetron + droperidol, and dexamethasone + droperidol, as well as most 5-HT$_3$ antagonist monotherapies.

4.2 Aprepitant Injectable Emulsion

Due to its surfactant additives, one concern with fosaprepitant is its association with infusion site adverse events, such as pain, erythema, and thrombophlebitis. Risk of anaphylaxis has also been reported [53]. Consequently, manufacturers recommended that fosaprepitant should be infused over 20–30 min [45].

An intravenous formulation of aprepitant (Cinvanti®) has recently been approved by the FDA for clinical use in CINV. This formulation consists of 130 mg aprepitant emulsified in a mixture of glycophospholipid, alcohol, and fatty acid [54].

Several studies have tested the safety profile of aprepitant emulsion as an intravenous push dose and found that it was well tolerated, with the most common adverse effects being headache and diarrhea [54–57]. As a result, aprepitant emulsion is licensed by the FDA for administration as an IV push dose over 2 min [58]. Aprepitant emulsion is currently only licensed for the prevention of CINV. There are no data on

its efficacy in preventing or treating PONV although trials are underway.

5 Rolapitant

Rolapitant has been approved for the prevention of CINV, for which the recommended oral dose is 180 mg. In addition, an injectable emulsion was later approved with a recommended dose of 166.5 mg infused over 30 min. It is longer acting compared to the other NK-1 receptor antagonists, with a half-life of up to 180 h, and can achieve maximum plasma concentration in 4 h. The oral bioavailability is 91% [59]. It is metabolized primarily by CYP-3A4 into its major circulating active metabolite M19 and excreted primarily in the feces [59]. Rolapitant appears to be effective when used as part of a multimodal prophylaxis regimen. Ahmed et al. [60] conducted a meta-analysis on the use of rolapitant as part of the multimodal prophylaxis for CINV and reported that the addition of rolapitant to 5-HT$_3$ antagonists plus dexamethasone significantly increased the complete response rate.

In open abdominal surgeries, rolapitant was found to reduce episodes of postoperative emesis in a dose-dependent manner. Preoperative oral administration of 20, 70, and 200 mg rolapitant was associated with significantly lower incidence of emesis than placebo 24 h after surgery. Furthermore, the 70 and 200 mg groups were significantly more effective than placebo up to 120 h after surgery. Higher doses of rolapitant may also be more effective than ondansetron in preventing PONV. The incidence of adverse events was found to be similar to that of placebo [61]. The long half-life of rolapitant could be beneficial in ambulatory surgery for the prevention of PDNV, but this will require further study.

6 Casopitant

Casopitant is available in both oral and intravenous formulations but has not been approved by the FDA. The oral formulation is well absorbed with a bioavailability of approximately 60%. The half-life of casopitant was estimated to be between 60 and 170 h and can reach maximum plasma concentration in 1 h. It is metabolized primarily by CYP3A4 into a hydroxylated metabolite M13 and excreted primarily in the feces [62].

In a study of high-risk women undergoing laparoscopic or laparotomic gynecologic surgeries or laparoscopic cholecystectomies, three different oral doses (50, 100, and 150 mg) were administered in addition to 4 mg ondansetron for PONV prophylaxis. All doses of casopitant were associated with significantly higher rates of 24-h complete response (defined as no vomiting, retching, rescue medication, or premature withdrawal); this could even be seen

up to 120 h. However, there was no significant difference among the groups in the proportion of subjects experiencing nausea. The incidence of adverse events was similar among all groups with the only notable difference being abnormalities in liver function tests occurring in 6% of patients in the 150 mg casopitant group [63]. Another study compared 50 mg of oral casopitant in combination with ondansetron to ondansetron alone in high-risk women. Similarly, a significantly greater proportion of subjects in the combination drug therapy group achieved complete response during the first 24 h after surgery. The combination drug therapy was well-tolerated but had a higher incidence of constipation and hypotension [64]. The network meta-analysis by Weibel et al. [10] reported that casopitant monotherapy has similar efficacy as aprepitant and fosaprepitant for PONV prophylaxis, while being more efficacious than ondansetron, granisetron, and dexamethasone as single-agent prophylaxis.

7 Vestipitant

In addition to oral formulation, vestipitant is also available as an intravenous formulation with doses of up to 48 mg. Unlike fosaprepitant, it could be rapidly infused in as little as 30 s without increased risk for injection site reaction, which makes it more suitable for use as a rescue anti-emetic [65]. Five different intravenous doses (6, 12, 18, 24, and 36 mg) were compared with ondansetron 4 mg for breakthrough PONV after failed ondansetron prophylaxis. Maximum plasma concentrations ranged from 204 to 809 ng/mL, time to maximum plasma concentration from 3 to 4 min, and half-life from approximately 5 to 9 h. All doses were found to be non-inferior in achieving complete response and have a similar safety profile as ondansetron. However, vestipitant was found to be superior in decreasing incidence of emesis and retching, with the use of rescue medication being the most common reason for treatment failure [66]. No other clinical study data have been published. Figure 1 illustrates the chemical structure of the various NK-1 antagonists and Table 1 summarizes the pharmacology of the drugs.

8 Other Study Drugs

Although no longer being further developed, many early study drugs have also shown efficacy in managing PONV. Vofopitant (GR205171) was the first NK-1 receptor antagonist to be investigated in a clinical study. It could be safely infused over 15 min with a half-life of approximately 8 h. Either a 25 mg intravenous dose or placebo was administered to subjects experiencing nausea or vomiting within 6 hours of undergoing abdominal or vaginal hysterectomy or ovariectomy. A greater proportion of subjects achieved

Table 1 Pharmacology of the NK-1 antagonists and the licensing status in the USA

Drug name	Licensing status	Route of administration	Recommended dose (mg, see licensed indication)	Half-life (h)	Elimination
Aprepitant [29]	Licensed for PONV	*Per os* (PO), bioavailability 60–65%	40 mg	9–13	Hepatic metabolism and biliary excretion
Aprepitant emulsion [79]	Licensed only for CINV	Intravenous (IV) push or infusion	130 mg	9–13	Hepatic metabolism and biliary excretion
Fosaprepitant [47]	Licensed only for CINV	Slow IV	150 mg	13.6	Hepatic metabolism and biliary excretion
Rolapitant [59]	Licensed only for CINV	PO, bioavailability 91% or	180 mg PO (70–200 mg was trialed in PONV)	138–205	Hepatic metabolism and biliary excretion
		IV	166.5 mg		
Casopitant [62]	Not licensed	PO or IV, bioavailability 60%	50 mg PO (50–150 mg was trialed in PONV)	60–170	Hepatic metabolism and biliary excretion
Vestipitant [65]	Not licensed	PO or IV	4–36 mg IV was trialed in PONV	5–9	Not available

CINV chemotherapy induced nausea and vomiting, *PONV* postoperative nausea and vomiting

complete response after 24 h with vofopitant. In addition, there was a lower incidence of emetic episodes, less severe nausea, and a decreased need for rescue medication. Finally, there was no significant difference in the incidence of adverse events between both groups [67]. CP-122721 was the first NK-1 receptor antagonist to be approved for clinical testing in North America. When used as prophylaxis before abdominal hysterectomy, both 100 and 200 mg oral doses decreased emetic episodes compared to placebo, while 200 mg alone or in combination with ondansetron decreased emetic episodes compared to ondansetron alone. In all of these groups, there was no significant difference in the proportion of subjects experiencing nausea. The only significant difference in adverse events was an increase in postoperative headache compared to placebo [68]. CP-99994 is another NK-1 antagonist, but so far has only been studied in animals [22, 69].

9 Role of NK-1 Antagonists in PONV Management

The network meta-analysis by Weibel et al. [10] has demonstrated that antiemetics vary considerably in their efficacy in preventing PONV. NK-1 antagonists are some of the most efficacious single-agent prophylaxes for PONV. Compared to the ondansetron plus dexamethasone combination, which is widely used in clinical practice, aprepitant has similar efficacy, while fosaprepitant is significantly more efficacious. In addition, several studies have demonstrated that NK-1 antagonists are efficacious as part of the multimodal PONV prophylaxis. In a high-risk patient cohort undergoing high-risk surgery, it is not uncommon for patients to develop

breakthrough PONV despite combination prophylaxis with 3 or 4 antiemetics [70]. In such cases, the higher intrinsic efficacy of NK-1 antagonists could confer additional therapeutic benefits, but this will require further studies. Utilization of aprepitant could benefit high-risk patients undergoing highly emetogenic surgeries, such as female non-smokers with a history of motion sickness undergoing laparoscopic pelvic surgery or patients with recurring PONV undergoing major surgery with expected perioperative opioid usage. The higher efficacy of NK-1 antagonists would also benefit cases where PONV could lead to catastrophic complications, such as neurosurgery, head and neck surgery, as well as gastric surgery [1].

NK-1 antagonist is one of the few antiemetic classes to have demonstrated efficacy as a rescue anti-emetic [66], with the others being 5-HT$_3$ antagonists [71] and antidopaminergics [72, 73]. 5-HT$_3$ antagonists are commonly used as the first-line PONV prophylaxis. According to PONV Consensus Guidelines, in patients developing PONV despite prophylaxis, repeated administration of antiemetic from the same class is unlikely to be successful [1]. With the development of the intravenous aprepitant formulation and other intravenous NK-1 antagonists, such as vestipitant, NK-1 antagonists may have a role as a first- or second-line rescue anti-emetic in patients receiving PONV prophylaxis.

Lastly, it is worth mentioning that several classes of antiemetics have overlapping adverse effects. 5-HT$_3$ antagonists and antidopaminergics are both associated with small risks of QT prolongation [74], while anticholinergics, antihistamine, and dexamethasone are all potentially deliriogenic in high-risk patients [75]. The most common adverse effects of NK-1 antagonists are headache, fatigue, and diarrhea [44, 45]; NK-1 is not associated with risks of

QT prolongation or delirium [76]. Therefore, NK-1 may have a niche in patients for whom the other antiemetics are contraindicated.

On the other hand, studies have reported that NK-1 antagonists may be more efficacious in preventing vomiting than nausea [28, 36, 63], which is nevertheless distressing for patients. This may result in proportionally smaller improvement in patient satisfaction [77].

10 Conclusion

Despite the knowledge in the connection between substance P, NK-1 receptors, and emesis, as well as the use of NK-1 receptor antagonists in chemotherapy-induced emesis, the use of NK-1 antagonists in the perioperative setting has been limited up until recently. NK-1 antagonists appear to be efficacious in preventing PONV, with effect size comparable to some combination therapies. There is also some evidence that NK-1 antagonists are efficacious as part of the multimodal PONV prophylaxis, but this is limited by the small number of relevant studies. Considering the continual paradigm shift towards multimodal PONV prophylaxis, this is an area that requires further study. While the perioperative use of NK-1 antagonists is currently limited due to acquisition costs and limited parenteral formulations, this will likely change with the availability of generic formulations and further research and development. NK-1 antagonists are invaluable additions to the repertoire of antiemetics for clinicians.

Declarations

Conflicts of interest/Competing interests Tong J. Gan received honoraria from Acacia, Edwards, Masimo, Medtronic and Merck.

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Code availability Not applicable.

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