

Management of postoperative nausea and vomiting: focus on palonosetron

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Abstract: Postoperative nausea and vomiting (PONV) remains a significant problem in modern anesthetic practice, with an incidence in high-risk groups of up to 80%. In addition to being unpleasant and distressing for the patient, PONV has the potential to adversely affect patient and surgical outcomes. Advances in PONV prophylaxis over recent years include using non-pharmacological means to reduce baseline risk, a change to less emetogenic anesthetic techniques and the combination of multiple antiemetic drugs. The 5-hydroxytryptamine-3 (5-HT₃) antagonists have proven a particularly valuable addition to the armamentarium against PONV. Palonosetron is a second-generation 5-HT₃ antagonist that has recently been approved for prophylaxis against PONV. It has unique structural, pharmacological and clinical properties that distinguish it from other agents in its class. This review summarizes current evidence on PONV prophylaxis, reviews the 5-HT₃ antagonists in particular and focuses on the established and future roles of palonosetron.

Keywords: palonosetron, antiemetics, 5-HT₃ antagonists, postoperative nausea and vomiting

Management of postoperative nausea and vomiting: an overview

Postoperative nausea and vomiting (PONV) is the most common complication of surgery and anesthesia. Both health care professionals and patients rate its avoidance and control of similar importance to that of alleviating pain.¹⁻⁴ In addition to patient dissatisfaction,⁵ PONV may have adverse consequences such as delayed recovery, unexpected hospital admission and delayed return to work of ambulatory patients. Rarely postsurgical morbidities such as wound dehiscence, pulmonary aspiration, surgical site bleeding and dehydration occur.⁶ Nausea occurs in approximately 20% of patients in the recovery room and in 50% thereafter, with vomiting in 5% and 25% respectively.⁷ Although children more than 3 years of age are at higher risk than adults,⁸ in some high-risk adult populations the incidence of PONV is 80% or more.^{9,10}

It is difficult to quantify the risk of PONV for any individual patient both because of the many pre-, intra- and postoperative factors that contribute to PONV and uncertainty about the relative impact of these potential influences. Activation of the vomiting center or the sensation of nausea may result from stimulation of the chemoreceptor trigger zone (eg, drugs, metabolic stimuli), the vestibular apparatus (motion), visceral afferent inputs (eg, gut distension or stasis, surgical stimulation of viscera, cardiovascular disturbance) and cortical inputs (eg, anxiety, pain, hypoxia, sensory stimuli, psychological associations, raised intracranial pressure). At least 3 nerves and 7 neurotransmitters are involved, making prophylaxis and treatment complex. In general a number of patient, surgical and anesthetic factors affect the risk of PONV⁶ and various patient risk assessment scores have been developed. The best known and validated is a simple 4-point score based mainly on patient characteristics. These are female gender, non-smoking habit, past history of

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motion induced or postsurgical nausea and vomiting, and postoperative opioid requirement.^{11,12} Prediction of outcome in the individual patient is imperfect, but management based on risk stratification of surgical sub-populations can reduce overall institutional rates of PONV.^{13,14} The duration of surgery (and anesthesia) is also a risk factor and some surgical procedures (eg, laparoscopy, strabismus surgery) are thought to confer higher risk, especially for nausea.^{15,16} Other established factors are younger patient age,^{6,16} higher intra- and postoperative opioid requirement^{6,17} and the type of anesthetic. Regional anesthesia is associated with a much lower risk than general anesthesia,¹⁶ with significant risk factors for the latter being maintenance with volatile agents rather than propofol,¹⁸ use of nitrous oxide^{19–21} and inadequate intravenous fluid loading.^{22–24}

Universal pharmacological prophylaxis against PONV is not warranted.^{25,26} If 30 of 100 people would feel sick or vomit after surgery and all 100 were given a prophylactic antiemetic drug, 10 would benefit and 90 would not, and 1 to 5 would suffer a mild side effect such as headache or sedation.²⁷ Therefore non-pharmacological strategies to reduce the baseline risk of PONV should be considered. Level I evidence supports techniques such as acupuncture, acustimulation or acupressure from wrist-bands applied at the Chinese P6 (Neiguan or Nei-Kuan) point near the wrist or at a number of Korean acupressure points on the fingers. These produce up to a one-third reduction in PONV, making them more effective than ondansetron against nausea, and they have an excellent side effect profile.^{28–30} Avoidance of general anesthesia or minimizing opioid requirement through the use of regional anesthesia might be appropriate,¹⁶ intravenous fluid (eg, 2 mL/kg for each hour of fasting) can be considered in ambulatory and high-risk inpatients,²⁴ nitrous oxide avoided,^{19,20} and propofol used for both induction and maintenance of general anesthesia (reciprocal of the absolute risk reduction or number-needed-to-treat [NNT] of 5 to prevent PONV within 6 hours of surgery).¹⁸ Using total intravenous anesthesia is as effective as giving a single antiemetic such as ondansetron.^{19,31} In addition a multimodal analgesic regimen should be used to minimize opioid dose requirements.¹⁷

The cost-benefit analysis of providing prophylaxis (rather than treatment) of PONV with antiemetic drugs is determined by the efficacy of the drug, its cost, and the consequences of the event. If the baseline risk is high, pharmacological intervention with a multimodal approach is justified.^{32,33} Approximately 20 drugs show efficacy, although only about 8 drugs are of proven reliability.²⁷ Of these, there is little

evidence that any one is better than another and most have a NNT of 4 to 7. This means, for example, that a reduction in risk of PONV from 80% to 60% represents a 25% relative risk reduction and a 20% absolute risk reduction or NNT of 5. When the baseline risk is only 10% a similar relative risk reduction produces an absolute risk reduction of only 2.5% and a NNT of 40.

Interventions that have proven ineffective for prophylaxis of PONV include ginger root and the cannabinoids,^{34,35} while intravenous (iv) metoclopramide 10 mg shows poor efficacy (no anti-nausea effect and NNT to prevent vomiting of 10).^{36,37} The antihistamine and phenothiazine drug classes (eg, promethazine 12.5–25 mg iv, dimenhydrinate 25–50 mg iv, prochlorperazine 5–12.5 mg iv, cyclizine 50 mg iv) show efficacy but clinical utility is limited, particularly in ambulatory surgical patients, because of sedation.^{38–43} Similar problems beset transdermal scopolamine⁴⁴ which also requires application at least four hours pre-operatively due to its slow onset. Side effects such as visual disturbance (number-needed-to-harm [NNH] of 5), dry mouth (NNH 12), dizziness (NNH 50) and agitation (NNH 100) tend to persist and limit its value, particularly in the elderly.

The butyrophenone droperidol remains the most cost effective drug for the prophylaxis of PONV in adults,^{45–49} despite recent issues relating to a ‘Black Box’ regulatory warning from the US Federal Drug Administration (FDA) in relation to possible cardiac conduction delay. It is cheap, has an NNT of 5 for both nausea and vomiting (NNT of 3 when added to patient-controlled intravenous morphine), with administration at the end of prolonged surgery recommended because of its short duration of action. Droperidol is one of the few antiemetic drugs to show a dose-response relationship.²⁷ Low doses (500 µg to 1.25 mg) are effective and minimize sedative and extrapyramidal side effects, both of which can be worrisome for children and ambulatory surgical patients.⁵⁰ Cardiovascular events are extremely unlikely, because QT prolongation in the antiemetic dose range is not significant,^{51,52} and as such its FDA warning has now been downgraded.

Dexamethasone 4 to 5 mg iv is a cheap, long acting antiemetic drug that shows efficacy against both nausea and vomiting (NNT 4).^{53–55} Early administration is recommended because it can prevent both early and late (up to 24 hours) PONV. After a single dose, dexamethasone appears to have an excellent side effect profile, although its effects on immune function, and the potential for adverse outcomes such as wound infection, have not been studied.

The 5-hydroxytryptamine-3 (5HT₃) receptor antagonists are popular prophylactic drugs and are considered in more

detail in the next section. The neurokinin-1 (NK1) receptor antagonists (aprepitant, rolapitant and casopitant) have an established indication for the prevention of chemotherapy-induced nausea and vomiting and are now also undergoing evaluation for PONV. These drugs appear particularly useful in preventing emesis. Aprepitant has recently been approved by the FDA for prophylaxis of PONV and preoperative oral aprepitant 40 mg has greater efficacy than ondansetron 4 mg IV against vomiting.⁵⁶

Patients thought to be at moderate or high risk of PONV should receive multimodal prophylaxis^{57,58} that includes 2 or 3 antiemetic drugs from different drug classes. Each drug is likely to result in a similar relative risk reduction, giving an additive but declining absolute effect.¹⁹ Many studies confirm the value of combining two or more antiemetic drugs and this has led to the propagation of evidence-based guidelines.^{59–64} Nevertheless, data on optimal dose combinations are scarce and lower doses than used for monotherapy may be effective.⁶⁵

The treatment of established PONV should be modified based on previous preventative measures and prophylactic drug therapies. Before management with antiemetic drugs, it may be possible to reduce symptoms by changing to an alternative analgesic or by adding adjuncts that reduce opioid dose consumption.⁶⁶ Surgical, mechanical or incidental causes of nausea and emesis should also be excluded. If the patient has not received prophylactic antiemetic drugs, many of these drugs will show efficacy as treatment at lower dosage than when used for prophylaxis (eg, iv ondansetron 1 mg or iv promethazine 6.25 mg).^{67,68} In general a rescue dose with a drug of the same class should not be given within 6 hours, and dexamethasone or scopolamine should not be repeated.⁶² Although potentially effective in some circumstances,^{69,70} sedative and anxiolytic drugs such as midazolam (1–2 mg and then 1–2 mg/h) or propofol (15–20 mg and then 15–20 µg/kg/min) are infrequently used for prophylaxis. However, they offer valuable treatment options^{71–73} and are as efficacious as iv ondansetron.^{70,73} If PONV appears specifically opioid-induced, low-dose naloxone (eg, 0.25 µg/kg/h) is also effective, without reversing analgesia.⁷⁴

5-hydroxytryptamine antagonists in the management of PONV

The potential value of 5-hydroxytryptamine (serotonin) receptor antagonists was discovered through the study of metoclopramide in the 1980s. The finding that, at high doses, metoclopramide showed activity at serotonin 'M' receptors (now known as 5-hydroxytryptamine type 3 [5-HT₃] receptors) led to the development of specific

receptor antagonists. Ondansetron was the first drug to become commercially available for PONV and has been followed by many others, including granisetron, dolasetron, tropisetron, ramosetron, azasetron and palonosetron. The 5-HT₃ antagonists compare favorably with other antiemetic drugs,⁷⁵ showing a NNT of 5 to 6 for prophylaxis against vomiting and 6 to 7 against nausea.^{67,76} Their efficacy is similar to droperidol or dexamethasone for the prevention of vomiting in adults,¹⁹ and their favorable side-effect profile has made them a popular choice in both adult and pediatric surgical populations. Because each of the 5-HT₃ antagonists shows a generally similar efficacy and side effect profile, the choice of drug is often governed by local availability and cost considerations.^{77–80} However knowledge of the differences in their pharmacokinetics, receptor affinity and pharmacogenetically-influenced responses allows a more objective approach to drug selection.

Mechanism of action

5-HT₃ receptors are found in the gut and in areas of the central nervous system associated with the regulation of nausea and vomiting, being abundant in the chemoreceptor trigger zone of the area postrema^{81,82} which has projections to the vomiting center located in the lateral reticular formation of the medulla oblongata. Stimulation of these receptors initiates the vomiting reflex.⁸³ Peripheral 5-HT₃ receptors are located in vagal nerve terminals, which are linked to the vomiting center via the nucleus tractus solitarius.⁸³ Competitive antagonism with 5-HT₃ receptor antagonists at these sites, and probably others, can block initiation of the vomiting reflex caused by emetogenic stimuli.

Pharmacokinetics

Azasetron (Serotone[®], Yoshitomi Pharmaceuticals) is licensed for PONV in Japan and Argentina. It is a benzamine derivative which exhibits potent and selective 5-HT₃ receptor antagonism. It has a terminal half-life of 6 to 8 hours and 60% to 70% of the active drug is excreted unchanged in the urine.⁸⁴

Dolasetron (Anzemet[®], Sanofi-Aventis) is a prodrug that is rapidly metabolized by carbonyl reductase (elimination half-life [$t_{1/2\beta}$] less than 10 minutes) to the active form hydrolosetron. Hydrolosetron ($t_{1/2\beta}$ 7 hours) is predominantly metabolized in the liver via the cytochrome P450 enzyme CYP2D6. Hydrolosetron is mainly (53%) excreted unchanged in the urine.⁸⁵

Granisetron (Kytril[®], Roche) is unique among the 5-HT₃ antagonists in that its liver metabolism is by the cytochrome P450 CYP3A isoenzyme. Its $t_{1/2\beta}$ is 5–8 hours, and 12% is excreted unchanged in the urine.⁸⁶

Ondansetron (Zofran[®], GlaxoSmithKline) has a relatively short $t_{1/2\beta}$ (3–5 hours) and undergoes extensive liver metabolism, primarily via the CYP3A4 isoenzyme, although CYP2D6 is an important secondary pathway. Some of its metabolites exhibit pharmacological activity but their plasma concentrations are too low to be clinically important. Five percent is excreted unchanged in the urine.⁸⁷

Ramosetron (Nasea[®], Astella Pharma) is licensed for use in Japan and Thailand, and has an additional indication for treatment of irritable bowel disease. It has a $t_{1/2\beta}$ of 4 to 9 hours, but a high receptor affinity prolongs its duration of action.⁸⁸

Tropisetron (Navoban[®], Novartis) undergoes extensive liver metabolism by the CYP2D6 isoenzyme. Its $t_{1/2\beta}$ is 8 hours, and 8% is excreted unchanged in the urine.⁸⁹

Pharmacodynamics

The duration of therapeutic effect of the various 5-HT₃ antagonists is influenced by factors other than the elimination half-life, and appears more closely associated with their binding affinity for the 5-HT₃ receptor.⁹⁰ Skin-flare testing, in which inhibition of cutaneous 5-HT₃ receptors is used as a surrogate marker, shows that some drugs have a longer clinical effect than their elimination half-life might suggest. For example cutaneous 5-HT₃ inhibition lasts 9 hours after ondansetron and more than 24 hours after a single intravenous dose (40 µg/kg) of granisetron.⁹¹ This probably reflects granisetron's high receptor affinity, demonstrated in vitro by the displacement of ondansetron but not granisetron by high receptor concentrations of 5-HT. Other 5-HT₃ antagonists with insurmountable receptor binding are tropisetron and palonosetron.^{92,93} Half-lives and receptor affinities for the various 5-HT₃ antagonists are shown in Table 1.

Table 1 Half-lives and 5-HT₃ receptor binding affinity for 5-HT₃ antagonists

Drug	Binding affinity (pK _i)	Half-life in healthy adult volunteers (h)
Azasetron	No data	6–8
Dolasetron ^a	9.8 ^b	6.9–7.3
Granisetron	8.42	4.9–7.7
Ondansetron	8.07	3.5–5.5
Ramosetron	8.5–9.0 ^b	4.3–9.0
Tropisetron	8.81	8
Palonosetron	10.4	40

^aValues are those of the active metabolite hydrolosetron.

^bAntagonist affinity (pA₂).

Pharmacogenetics

Various genetic factors influence an individual's response to drugs and genetic polymorphism plays a role in the metabolism, transport and receptor binding of the 5-HT₃ antagonists.

CYP2D6 genetic polymorphism

Phase I metabolism of the 5-HT₃ antagonists occurs in the liver by the cytochrome P450 enzyme system, the most important isoenzyme for which is cytochrome P4502D6 (CYP2D6). This isoenzyme is responsible for the metabolism of many drugs⁹⁴ and there is significant inter-individual variability in its activity. The gene encoding CYP2D6 lies on chromosome 22q13.1^{95,96} and gene variants can alter enzymic activity, such that individuals can be classified as poor, intermediate, extensive and ultra-rapid metabolizers. Most of the population have the 'wild-type' 2D6 allele and are extensive (normal) metabolizers.⁹⁷ Ultrarapid metabolizers typically display gene duplications and the resultant increase in enzyme activity may lead to sub-therapeutic plasma concentrations despite usual doses.⁹⁸ Ethnic variability in the prevalence of ultra-rapid metabolizers is pronounced, varying from a low incidence in Caucasians (2%), 7% in parts of Spain (possibly due to Moorish colonization prior to the 15th century), to 20% to 29% in Arabic countries and Ethiopia.^{94,99–101}

Although the CYP2D6 system is the dominant metabolic pathway for the 5-HT₃ antagonists such as dolasetron, tropisetron and palonosetron, it is less influential for ondansetron which is primarily metabolized by CYP3A4. Granisetron's metabolism is entirely independent of CYP2D6, undergoing transformation by CYP3A (Table 2).

Table 2 Metabolism of 5-HT₃ antagonists

Drug	Primary pathway	Secondary pathway
Dolasetron ^a	CYP2D6	CYP3A
Granisetron	CYP3A	CYP3A4
Ondansetron	CYP3A4	CYP1A2 CYP2D6 CYP2E1
Ramosetron	CYP1A2	CYP2D6 CYP1A1
Tropisetron	CYP2D6	CYP3A4 CYP2E1
Palonosetron	CYP2D6	CYP3A4 CYP1A2

^aValues are those for the active metabolite hydrolosetron.

Genetic polymorphisms of CYP2D6 can influence clinical efficacy. Higher rates of vomiting occur in ultrarapid metabolizers treated with tropisetron (and to a lesser extent ondansetron) than in extensive or poor metabolizers.^{102,103} In contrast granisetron is unaffected by ultrarapid metabolizer status, and despite palonosetron undergoing CYP2D6 metabolism a small study found no difference in efficacy between poor and extensive metabolizers (although no ultrarapid metabolizers were investigated).⁹⁰ Genetic testing may identify individuals who are less likely to respond to certain 5-HT₃ antagonists, but screening is only likely to be helpful in high-risk ethnic populations.⁹⁸

5-HT₃ receptor genetic polymorphism

The 5-HT₃ receptor is a ligand-gated cation channel with a pentameric structure. Five subunits enclose an ionopore modulating passage of ions such as calcium when activated by binding of serotonin. A number of polymorphisms of the gene coding for the 5-HT_{3B} subunit exist, and oncology patients who are homozygous for an AAG deletion have a poorer response to tropisetron and ondansetron.¹⁰⁴ The extent to which receptor polymorphism influences the efficacy of other 5-HT₃ antagonists remains unclear, another study finding no difference in the antiemetic efficacy among patients with different polymorphisms of the 5-HT_{3A} receptor subunit.¹⁰⁵

ABCB1 transporter genetic polymorphism

The adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) transporter (also known as P-glycoprotein or MDR-1) functions as a transmembrane efflux pump in many tissues. It is responsible for the physiological transportation of a variety of drugs, including the 5-HT₃ antagonists. A single-nucleotide polymorphism at position 3435 of the ABCB1 gene has shown limited influence on 5-HT₃ antagonist efficacy. One study of granisetron, ondansetron and tropisetron found improved short-term (with a trend towards long-term) efficacy of granisetron in *ABCB1 3435 TT* individuals compared to *ABCB1 3435 CC* or *CT* genotypes.¹⁰⁶ This finding may reflect higher CNS levels of granisetron due to improved drug transport, but further studies are required.

Clinical efficacy

The anti-vomiting effect of this class of drugs is greater than the anti-nausea effect⁷⁶ and there is a 25% overall risk reduction for PONV.^{19,67} This makes the 5-HT₃ antagonists cost effective for prophylaxis in high-risk patients, and although droperidol

is cheaper and equally effective in adults, ondansetron prevents vomiting more effectively in children.³⁷

The maximum recommended doses for single drug prophylaxis are 8 mg iv or 16 mg orally for ondansetron,¹⁰⁷ 12.5 mg IV for dolasetron,^{108,109} 1 mg iv for granisetron¹¹⁰ and 5 mg iv for tropisetron.¹¹¹ If the patient has not received prophylaxis a smaller iv dose (eg, ondansetron 1 mg, granisetron 0.1 mg or tropisetron 0.5 mg) is recommended for treatment.^{63,67} The NNT to prevent another episode of nausea or vomiting within 24 hours is 4 to 5.¹¹²

Adverse effects

The 5-HT₃ antagonists have an enviable safety profile, with most side effects (eg, headache, constipation and asthenia) mild and transient. The NNH for ondansetron is 36 for headache, 31 for elevated liver enzymes and 23 for constipation.⁷⁶

The cardiovascular and ECG effects are of particular interest since the saga of the (now reversed) FDA “Black Box” warning about droperidol and cardiac risk due to prolongation of the QT interval. All 5-HT₃ antagonists block cardiac sodium ion channels *in vitro*¹¹³ and thus have the potential to alter cardiac conduction. Safety studies in healthy volunteers indicate a transient increase in PR, QRS and QTc intervals after dolasetron¹¹⁴ and prolonged QTc intervals after ondansetron,⁵² however a single dose of a 5-HT₃ antagonist is considered unlikely to cause cardiovascular effects⁸¹ and meta-analysis shows monotherapy or combined therapy has a similar safety profile to droperidol or dexamethasone.¹¹⁵

Palonosetron

Background

Palonosetron (Aloxi®, MGI Pharma) is the latest 5-HT₃ antagonist licensed and the only drug of its class approved for prophylaxis against both acute and delayed chemotherapy-induced nausea and vomiting (CINV). Its unique properties have led to it being described as the first of a ‘second-generation’ of 5-HT₃ antagonists. Far higher receptor affinity and a much longer half-life than other 5-HT₃ antagonists confer a prolonged duration of action. Following successful Phase III clinical trials the FDA approved its use for prevention of PONV in March 2008.

Chemical structure and binding

Traditional 5-HT₃ antagonists are based on a 3-substituted indole ring which mimics the structure of serotonin. In contrast palonosetron is a single stereoisomer isoquinoline

based on a fused tricyclic ring system attached to a quinuclidine moiety (Figure 1). This novel chemical structure may explain some of the differences in its receptor affinity, interaction and binding.

Pharmacokinetics

The pharmacokinetic profile of palonosetron has been evaluated in healthy volunteers^{116,117} and cancer patients.¹¹⁸ A single dose of 10 µg/kg iv is widely distributed in the tissues (mean ± SD volume of distribution 8.3 ± 2.4 L/kg). Palonosetron is moderately bound to plasma proteins (62%)¹¹⁹ and despite its extensive distribution, little is sequestered in erythrocytes.¹¹⁷

In keeping with most 5-HT₃ antagonists, the metabolism of palonosetron is primarily in the liver by the cytochrome P450 enzyme system, with CYP2D6 the predominant isoenzyme and CYP3A4 and CYP1A2 of secondary importance.¹¹⁹ The main metabolites, *N*-oxide-palonosetron, 6-(*S*)-hydroxy-palonosetron and small amounts of 6-keto-*N*-oxo-palonosetron display less than 1% of palonosetron's activity at 5-HT₃ receptors.¹¹⁷ Although a small study (n = 6) comparing poor against extensive metabolizers of CYP2D6 substrates found no difference in efficacy,^{90,119} palonosetron has not been studied in ultrarapid metabolizers so it is possible that in this genotype it has reduced efficacy.

Following initial rapid distribution, iv palonosetron undergoes a slow elimination phase, primarily handled by the kidney, with 83% of a 10 µg/kg dose being recovered from

the urine after 240 hours¹¹⁷ and 40% of the administered dose excreted unchanged. Total body clearance of palonosetron in healthy subjects is approximately 160 ml/h/kg, with renal clearance approximately 66.5 mL/h/kg. This slow elimination results in a long terminal half-life of approximately 40 hours,^{116,117} which contrasts with previous 5-HT₃ antagonists such as ondansetron (3–5 hours) and granisetron (5–8 hours) (see Table 1).

Pharmacokinetic studies show that the characteristics of palonosetron in healthy volunteers and elderly patients with cancer are similar^{116–118} and widespread clinical experience in the CINV setting confirms that no dose adjustment is necessary in elderly patients.^{119,120} In addition, mild to moderate renal impairment or hepatic impairment do not affect its pharmacokinetic parameters and dose modification is unnecessary.¹¹⁹

There is currently no clinical experience with palonosetron in pregnant or lactating women. Studies of teratogenicity in animal models show no evidence of interference with fertility or fetal development, but caution is advised until safety in these populations is established.¹¹⁹ There is little experience to date to determine the safety of palonosetron in children, however emerging evidence suggests that it is effective and appears safe.¹²¹

Pharmacodynamics

Receptor binding is thought to be the most important factor influencing the duration of action of the 5-HT₃ antagonists.

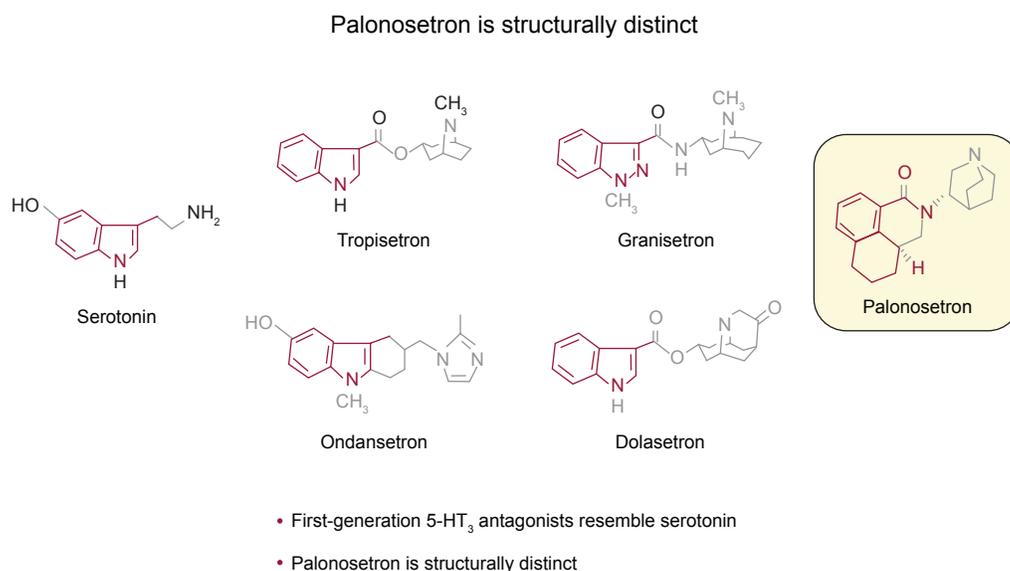


Figure 1 Structures of palonosetron and other 5-HT₃ antagonists.

Reproduced with permission from Rojas C, Grunberg S, Rosti G. 2007. Creating real benefit for patients at risk of nausea and vomiting: palonosetron—from bench to bedside. *Clin Adv Hematol Oncol*, 5(12 Suppl 19):1–20.¹²² Copyright © 2007 Millenium Medical Publishing.

Palonosetron shows avid binding to the 5-HT₃ receptor, with a pK_i of 10.4,⁹³ which far exceeds other 5-HT₃ antagonists. This binding affinity is more than 30 times the potency of granisetron and 100 times that of ondansetron (Table 1). In addition, in isolated specimens binding is insurmountable by the addition of increasing concentrations of agonist, which suggests that palonosetron is not simply a competitive antagonist at the 5-HT₃ receptor.⁹³ High receptor affinity is accompanied by high selectivity, with low affinity (pK_i < 6.0) demonstrated for various other receptors including 5-HT_{1A,1D,2A,2C}.⁹³ This makes it unlikely that palonosetron will produce unwanted effects at other receptor sites.

Emerging evidence indicates that palonosetron interacts at the 5-HT₃ receptor in a different manner to previous 5-HT₃ antagonists. The chemical structure is dissimilar to serotonin, so palonosetron may bind to the 5-HT₃ receptor at an allosteric site, different to other antagonists that bind at the orthosteric site occupied by serotonin.¹²² This interaction at the allosteric site may prevent attachment of serotonin at its orthosteric site, explaining the insurmountable binding noted in vitro. Furthermore studies of calcium influx in specimens exposed to and then washed clear of palonosetron show continued receptor occupation well beyond that predicted by controls and far in excess of that shown by granisetron and ondansetron.¹²³ The investigators ascribe this to possible internalization of the 5-HT₃ receptor following exposure to palonosetron.

Adverse effects

Side effects

Observation of side effects during the clinical development of palonosetron indicated a similar safety profile to other 5-HT₃ antagonists, the most common side effects being non-serious and short duration headache (9%), constipation (5%) and dizziness (1%)¹¹⁹ (Table 3). Post-marketing surveillance data after over 1 million patient exposures confirms the safety of palonosetron, with few serious adverse events reported

(n = 81, 0.0061%), most frequently headache (n = 13), hypersensitivity reactions (n = 8) and injection site burning or discomfort (n = 8).¹²⁴

Cardiac conduction

The potential for a delay in cardiac conduction, in particular QTc prolongation, was evaluated in Phase III studies. In common with other 5-HT₃ antagonists, palonosetron slightly increases QTc intervals, the mean increase after a bolus dose lying between 1 and 3 ms.^{125–127} This compares favorably with a 5 ms increase after ondansetron^{125,127} and a 5.4 ms increase after dolasetron.¹²⁶ Palonosetron has been safely administered to many patients with cardiac impairment although the prescribing information advises caution in patients at risk of QTc prolongation.¹¹⁹

Drug interactions

Palonosetron does not cause inhibition or induction of the main hepatic enzyme systems including CYP2D6, CYP1A2 and CYP3A4/5, so the risk of significant drug interactions is low.¹¹⁹ However an adverse reaction with apomorphine that presented as profound hypotension and altered consciousness has been reported, so concomitant use is contraindicated.¹²⁸

Therapeutic efficacy

The following definitions have been used in trials describing palonosetron's therapeutic efficacy: complete response (CR) – no rescue medication, no emesis; complete control (CC) – no rescue medication, no emesis, no more than mild nausea; treatment failure – episode of emesis, or rescue medication administered; early nausea and vomiting – 0 to 24 hours; delayed nausea and vomiting –24 to 120 hours.

Chemotherapy-induced nausea and vomiting

Most clinical experience with palonosetron has been in the setting of the management of CINV, with over 5 million doses having been prescribed. For the purpose of this review,

Table 3 Adverse reactions of palonosetron, ondansetron and dolasetron

Event	Palonosetron 0.25 mg (n = 633)	Ondansetron 32 mg (n = 410)	Dolasetron 100 mg (n = 194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (<1%)	4 (1%)	4 (2%)
Abdominal pain	1 (<1%)	2 (<1%)	3 (2%)
Insomnia	1 (<1%)	3 (1%)	3 (2%)

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key outcomes only are described. In a phase II dose-ranging study¹¹⁸ complete response rates were highest in the 3 to 90 µg/kg groups and there was no dose-related increase in side effects. Consequently 0.25 mg and 0.75 mg (equivalent to 3 and 10 µg/kg respectively) doses were evaluated in phase III trials as minimum effective doses. The recommended initial treatment dose for CINV is now 0.25 mg.

For the control of early CINV (ie, 0–24 hours), phase III studies found that palonosetron compared favorably with dolasetron and ondansetron. Palonosetron 0.25 mg or 0.75 mg or dolasetron 100 mg resulted in similar complete response rates of 63%, 57% and 53% respectively. However, the palonosetron 0.25 mg group had fewer episodes of emesis and more patients free of emesis compared with the dolasetron group.¹²⁶ In a comparison of palonosetron 0.25 mg, 0.75 mg or ondansetron 32 mg, palonosetron 0.25 mg was associated with a higher early complete response rate than ondansetron and fewer emetic episodes.¹²⁵

In the 24–120 hour period palonosetron 0.25 mg and 0.75 mg were superior to dolasetron 100 mg for complete response rates (54%, 57% and 39%, respectively) and for complete control (48%, 52% and 36%, respectively).¹²⁶ The complete control rates were higher with palonosetron on days 2 and 3 post administration and on day 4 after the higher dose. The number of patients free of nausea was also higher in both palonosetron groups and time to first emetic episode or treatment failure was longer, with most patients not requiring rescue medication until more than 2 days after their single dose. Similar results were seen in the comparison with ondansetron 32 mg.¹²⁵ A pooled analysis of these trials found early CINV was an important predictor for delayed CINV¹²⁹ but that patients without early CINV receiving palonosetron were less likely to get delayed CINV compared with dolasetron and ondansetron. Conversely patients who experienced early CINV despite palonosetron were more likely to be protected against delayed CINV (23%) than those taking dolasetron or ondansetron (12%). Therefore, as well as showing early efficacy, palonosetron seems to confer additional protection against delayed CINV.

Combination therapy using palonosetron with antiemetic drugs of other classes appears safe and effective.¹³⁰ Palonosetron 0.25 mg and dexamethasone 8 mg produced high early complete response rates (84%), falling to 59% for late CINV. Only 3% to 13% of patients complained of more than mild nausea during days 0 to 5. In one study comparing palonosetron with ondansetron the early complete response rate did not differ overall, but among those also given dexamethasone complete response rates were improved

in the 24- to 120-hour period in the palonosetron group.¹²⁷ Triple therapy prophylaxis using aprepitant, dexamethasone and palonosetron 0.25 mg resulted in high rates of early efficacy (complete response 88%, no emesis 93% and no nausea 71%). These benefits extended into the ‘delayed CINV’ period and only 0% to 5% of patients rated their nausea as severe.¹³¹ A double-blinded, placebo-controlled, randomized pilot study was terminated after an interim analysis showing unacceptable early and delayed CINV in patient groups receiving palonosetron and dexamethasone in whom aprepitant was not also given.¹³² Good efficacy has been reported with this triple therapy combination given on day 1 only, the incidence of no emesis reported as 97% to 100% over 5 days.¹³³

Multiple-day dosing with palonosetron 0.25 mg on alternate days appears effective but has not been adequately evaluated compared with a single dose.^{134,135}

Palonosetron for PONV Optimum dosing

Two placebo-controlled randomized studies have evaluated palonosetron across a range of doses for prophylaxis against PONV. Three hundred and eighty-one women undergoing major gynecological surgery were randomized to doses between 0.1 µg/kg and 30 µg/kg or placebo.¹³⁶ 1 µg/kg and 30 µg/kg doses produced a significantly better complete response in the first 24 hours (44% ($p = 0.004$) and 45% ($p = 0.002$) vs 19%) and a lower incidence of nausea during the same period. The second study compared 0.025 mg, 0.05 mg, and 0.075 mg doses of palonosetron in 546 patients with a simplified Apfel risk score for PONV of ≥ 2 ^{9,11} undergoing laparoscopic surgery.¹³⁷ Only the highest 0.075 mg dose showed a significantly improved rate of complete response compared with placebo in the 0–6 hour, 0–24 hour and 0–72 hour periods (49% vs 37%; 43% vs 26%; 39% vs 24% for each period respectively, $p < 0.05$). Patients receiving 0.075 mg were also less likely to report functional interference (eg, with appetite, enjoyment of life, social life) because of PONV experienced in the first 24 hours. Based on these two studies, the minimum effective dose of palonosetron in the setting of PONV is 0.075 mg, and this dose has been approved by the FDA for PONV prophylaxis.

Early PONV

Two identically designed multi-center double-blind placebo-controlled Phase III efficacy trials were published recently.^{138,139} Both trials included early PONV amongst

their primary and secondary endpoints. In one study¹³⁸ 544 patients who were at least a moderate risk of PONV (Apfel risk score ≥ 2) undergoing inpatient gynecological or breast surgery were given palonosetron 0.025 mg, 0.05 mg, 0.075 mg or placebo. All patients received nitrous oxide as part of their anesthetic and no other prophylactic antiemetic drugs. There was a dose-dependent increase in complete response in the 0-to 24-hour period, with rates for the placebo, palonosetron 0.025 mg, 0.05 mg and 0.075 mg groups being 36%, 46% ($p = 0.073$), 47% ($p = 0.069$) and 56% ($p = 0.001$), respectively (Figure 2). The incidence of emesis was significantly reduced in the palonosetron 0.075 mg group compared with placebo (40.0% vs 60.3%, $p = 0.001$), as was the incidence of nausea (49.6% vs 70.6%, $p = 0.001$). The severity of nausea (graded as none, mild, moderate, severe) was lower with all three doses of palonosetron.

In the other study¹³⁹ 574 patients with Apfel score ≥ 2 and undergoing day-case laparoscopy received prophylaxis against PONV with palonosetron 0.025 mg, 0.05 mg, 0.075 mg or placebo. Nitrous oxide was used but no other prophylactic antiemetics were administered. A similar dose-dependent increase in complete response was observed, with rates in the 0- to 24-hour period for the placebo, palonosetron 0.025 mg, 0.05 mg and 0.075 mg groups of 26%, 33% ($p = 0.187$), 39% ($p = 0.017$) and 43% ($p = 0.004$), respectively (Figure 2). The incidence of early emesis was lower in the palonosetron 0.075 mg group compared with placebo (33% vs 44%, $p = 0.075$), as was the severity of nausea ($p = 0.036$).

These studies confirm that palonosetron 0.075 mg provides effective prophylaxis against acute early PONV. The relative risk reduction of 20% to 30% is of a magnitude comparable to that with other single-agent interventions.¹⁴⁰

Delayed PONV

Both the phase III studies detailed above also evaluated the incidence of PONV in the delayed (24- to 72-hour) and 'postdischarge' (6- to 72-hour) periods. Kovac et al found complete response rates for placebo, palonosetron 0.025 mg, 0.05 mg and 0.075 mg of 43%, 53%, 52% and 66% ($p < 0.05$) respectively during the 6- to 72-hour period, and 52%, 56%, 61% and 70% ($p = 0.002$), respectively, during the 24- to 72-hour period¹³⁸ (Figure 3). The time to treatment failure was significantly prolonged in the palonosetron 0.075 mg group ($p = 0.004$), and the median time to first emesis was more than 72 hours after palonosetron 0.05 mg ($p = 0.014$) and 0.075 mg ($p = 0.002$) (compared with 3.9 hours after placebo). The severity of nausea was less in the 6- to 72-hour period for the palonosetron 0.075 mg group ($p = 0.011$).

Complete response rates in the Candiotti et al study for placebo, palonosetron 0.025 mg, 0.05 mg and 0.075 mg were not significantly different over the 24- to 72-hour period (Figure 3), and 34%, 38%, 39% and 45% ($p = 0.064$) respectively for the 6- to 24-hour period.¹³⁹ The dose-dependent increase in complete response with increasing palonosetron dosage did not reach statistical significance but was present with respect to delay of treatment failure. Although the incidence of late

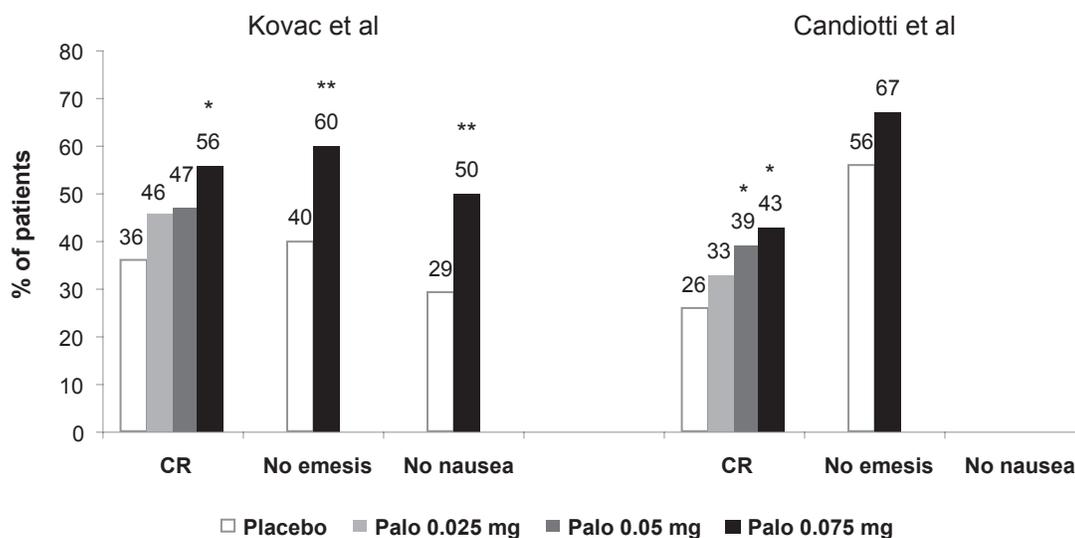


Figure 2 0- to 24-hour PONV: complete response (CR), no nausea and no emesis.

* $p < 0.017$; ** $p < 0.05$.

Data derived from Kovac et al 2008¹³⁸ and Candiotti et al 2008.¹³⁹

Abbreviations: Palo, palonosetron; PONV, postoperative nausea and vomiting.

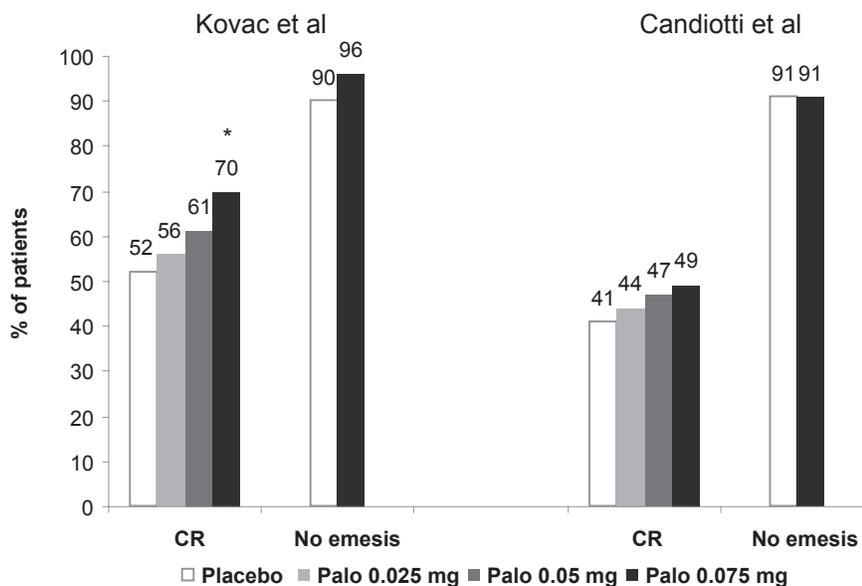


Figure 3 24- to 72-hour PONV: complete response (CR) and no emesis.

* $p < 0.017$.

Data derived from Kovac et al 2008¹³⁸ and Candiotti et al 2008.¹³⁹

Abbreviations: Palo, palonosetron; PONV, postoperative nausea and vomiting.

emesis did not differ between the groups, there was a reduction in the intensity of nausea in the palonosetron 0.075 mg group for the 6- to 72-hour period ($p = 0.036$).

These findings confirm that palonosetron, at a dose of 0.075 mg, improves the control of nausea and vomiting into the second and third days post operatively, an effect that may be most marked after major operations requiring inpatient stay. Palonosetron 0.075 mg also reduces the severity of delayed nausea, which may be of particular relevance to the day-surgery population for whom it is difficult to identify those at risk of postdischarge PONV and for whom early return to normal activities is important.¹⁴¹ Of note, palonosetron also seems to have a prolonged effect in reducing the severity of nausea, a feature not shared by other 5-HT₃ antagonists. However the magnitude of effect against PONV appears to be similar to that of other established drugs following inpatient surgery in moderate- or high-risk groups, and modest against delayed PONV in ambulatory surgical patients with shorter and lower postoperative opioid requirements, so more evidence is required before a role against postdischarge PONV in the day-care setting can be recommended.

Discussion

Approval of palonosetron for the prevention of PONV provides another therapeutic intervention in the arsenal against the 'big little problem'.¹⁴² The prolonged half-life and very strong affinity of palonosetron for the 5-HT₃ receptor

provide the pharmacological basis for a long duration of action that appears to far exceed that of other 5-HT₃ antagonists. Clinical effectiveness into the fifth day after chemotherapy has been demonstrated, and after surgery prolonged effectiveness is also of potential value because PONV often presents late or after discharge.¹⁴¹ Palonosetron is an established antiemetic drug in oncology medicine, where it shows better efficacy against both early and delayed CINV than other 5-HT₃ antagonists. This prolonged clinical effect combined with superior efficacy against PONV mitigates a traditional obstacle for a newly developed drug – its cost. A recent theoretical evaluation suggested its cost effectiveness compared favorably with ondansetron.¹⁴³ However the etiology of CINV, which involves a large release of serotonin from the enterochromaffin cells in the small intestine in response to chemotherapeutic agents, is different to that of PONV, which has multi-factorial aetiology. It remains to be seen whether the same degree of efficacy can be expected in the postsurgical setting.

The role of combination therapy in patients at high risk of PONV has been well established.^{19,57,58} On the basis of promising results for combination therapy with palonosetron in CINV, similar studies in the surgical population will no doubt be undertaken. The effectiveness of palonosetron and dexamethasone, particularly against nausea, may dovetail well with the antiemetic properties of the neurokinin-1 antagonists such as aprepitant. Future research needs to be directed towards comparisons of the efficacy of palonosetron

and other 5-HT₃ antagonists, towards establishing suitable drug and drug dose combinations to prevent PONV in high-risk patient groups (including cost-effectiveness evaluation). Investigation of its efficacy for the treatment of PONV is also required. Although the clinical value of palonosetron in this setting has yet to be established, the pre-marketing evidence suggests it may be a valuable addition to the pharmacological armamentarium.

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