

Research Review

PRODUCT REVIEW

Granisetron tablets (Granirex)

About the Reviewer



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John Childs was the National Clinical Director, Cancer at the Ministry of Health for 7 years until 2012, and has been a specialist in radiation oncology with the Auckland District Health Board since 1991. He has also held appointments as Clinical Director of Radiation Oncology and Clinical Leader of Medical Services. He also consults at Auckland Radiation Oncology in Auckland and at a satellite clinic in Whangarei. John has held various national roles including a member of the Cancer Control Council, the chair of the National Cancer Treatment Working Party and a number of other national advisory committees. He is currently chair of the National Bowel Cancer Screening Advisory Group. He has also been a council member for the Royal Australasia and New Zealand College of Radiologists (RANZCR), a board member of the Faculty of Radiation Oncology, and an examiner in radiation oncology for the RANZCR. He has a particular interest in urological, gastrointestinal, haematological, chest malignancies and palliative radiation oncology.

ABBREVIATIONS USED IN THIS REVIEW

(CI/RI/PO)NV = (chemotherapy-induced/RT-induced/postoperative) nausea and vomiting
IV = intravenous
OR = odds ratio
RCT = randomised controlled trial
RT = radiotherapy
TBI = total body irradiation

Chemotherapy, RT and surgery can be associated with troublesome NV. This review presents a review of evidence in support of the newly-funded granisetron tablets (Granirex) for the prevention and treatment of CINV, RINV and PONV. Antiemetic agents available for the prevention and treatment of these conditions in NZ are summarised and described, after which the properties and details of granisetron are described. Details on the emetogenic potentials of different chemotherapeutic treatments are also provided, followed by evidence for the use of granisetron, including findings of important RCTs and meta-analyses. The international recommendations for managing CINV, RINV and PONV are presented and discussed in the context of the NZ setting.

Incidence/prevalence of CINV, RINV and PONV

NV can be a distressing adverse effect with chemotherapy, RT and surgery, due to the toxic nature of the agents/procedures.¹⁻⁴ Although vomiting and nausea are related, they may occur via different mechanisms. Stimulation of neurotransmitter receptors in the chemoreceptor trigger zone, the vomiting centre in the medulla and gastrointestinal tract can trigger a multistep reflex pathway that culminates in vomiting to remove 'poisons' from the stomach. Nausea is a subjective sensation of an urge to vomit without the muscular movements required to expel the contents of the stomach. An unproductive attempt at vomiting is commonly termed 'retching'. An emetic episode is an episode of vomiting or retching.

Chemotherapeutic agents and their metabolites are usually toxic to normal human physiology, and as such elicit responses similar to other poisons, including NV via activation of neurotransmitter receptors, primarily serotonin (5-HT₃) and dopamine.^{1,3} Emesis due chemotherapy and radiotherapy may be due to induction of serotonin release from small intestinal cells. CINV can be immediate (30–120 minutes after chemotherapy administration), acute (≤24 hours) or delayed (>24 hours), with the latter not uncommon. The incidence of CINV varies significantly from >90% to <10% depending on the types and combinations of agents used (see section 'Emetic risk groups' for more detail).

Anticipatory NV is a conditioned response that occurs prior to planned chemotherapy administration following a previous negative experience, and often affects younger patients due to having received more aggressive chemotherapy. Vomiting despite prophylactic treatment that requires rescue antiemetic agents is referred to as breakthrough emesis, while emesis during treatment cycles when antiemetic prophylaxis and/or rescue therapy have failed in earlier cycles is referred to as refractory emesis.

The cause of RINV is not fully understood, although it may be caused by damage to rapidly dividing cells in the small intestine with abdominal RT. However, the mechanisms of RINV after RT to other sites is largely unknown, but are thought to be similar to CINV.^{2,5} RINV is characterised by a latent asymptomatic 1- to 2-hour period after RT, followed by a 6- to 8-hour period of NV, although one study has reported a median time of 3 days for a first episode of NV following radiotherapy.⁶

Large observational studies have reported that 50–80% of patients undergoing RT may experience NV, although the incidence is now less than one-third of patients because of improved radiation techniques with more accurate targeting of radiation to reduce radiation dose to sensitive structures and increased use of antiemetics.^{2,5-8} RT to the whole body or upper abdomen is associated with higher rates of NV than RT to other areas, and the risk of RINV is increased when larger volumes are irradiated or larger doses per fraction are used.^{3,8} Reports have suggested that the majority of patients who experience RINV are not prescribed antiemetics.

PONV is the most common complication during the immediate postoperative period. The overall incidence of PONV is estimated at ~25–30% (40–50% nausea, 25–30% vomiting) across all surgical patients,⁹ but depends on the specific surgical population studied, with certain high-risk populations (e.g. tonsillectomy, strabismus, laparoscopy patients) having incidences as high as 70–80% in the absence of prophylactic antiemetic therapy. The use of volatile anaesthetics (e.g. sevoflurane, desflurane), nitrous oxide and opioids also increases the risk of early PONV (2–6 hours postsurgery), while opioid use and motion sickness due to transport have been implicated in late PONV (24–48 hours postsurgery).¹⁰ Utilising regional or total IV anaesthesia can help to lower the risk of early PONV. Females, nonsmokers, younger patients and those with a prior history of PONV or motion sickness are also at increased risk of PONV.

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Burden of NV

NV can lead to dehydration, electrolyte imbalances, bodyweight loss, malnourishment, epigastric pain, oesophageal bleeding, hiccups and anticipatory NV. Depression can result, which may contribute to general apathy, fear and isolation.^{1,3,9} NV also has significant impacts on quality of life, functioning and costs.^{2-4,9} Control of CINV and RINV is important to enable anticancer treatment to continue; controlling NV can significantly improve the tolerability of chemotherapy and enable completion of planned treatment courses. Moreover established vomiting can become refractory to simple treatments, so prevention and, failing that, early intervention are important.

While there has been a decrease in unexpected hospital admissions due to PONV, they still occur in ~0.5–2% of patients. Overall it has been reported that healthcare costs from PONV have increased due to unanticipated admissions, increased nursing care and delayed discharge from the postanesthesia care unit or hospital.⁹

It is important that patients' NV is adequately managed with antiemetics to reduce distress, particularly when persistent delayed nausea is present.¹ While there are many antiemetic agents available (see Table 1), many patients are still affected. In the case of RINV, this may be due to radiation oncologists not considering RINV as a serious concern, and underprescribing of prophylactic antiemetics for RINV has been reported.^{2,6,8} A web-based survey of oncologists prescribing RT, which included NZ oncologists, showed variation in risk estimates and management strategies, particularly for low- and moderate-risk RT cases, and the authors concluded that RINV is understudied.¹¹ One study has reported that one-third of patients who experienced RINV would have liked antiemetic treatment.⁸ Similarly, inconsistency with antiemetic guidelines in CINV has also been reported.¹²

Available antiemetics for preventing and managing NV in NZ

Over the last two decades, new effective antiemetic agents have been introduced, including 5-HT₃ (5-hydroxytryptamine; serotonin) receptor antagonists, NK1 (neurokinin-1) receptor antagonists and other agents, including corticosteroids.⁴ In NZ, a number of antiemetics from several classes are available (Table 1).¹ Antihistamines, anticholinergics and 5-HT₃ antagonists act on the emetic centre, benzamines act on the chemoreceptor trigger zone, antihistamines and corticosteroids act on the cerebral cortex (corticosteroids also have other unknown sites of action), and metoclopramide and 5-HT₃ antagonists act peripherally. Ondansetron tablets and injections and tropisetron injections had been the only 5-HT₃ antagonists funded by Pharmac NZ.¹³ However, as of Nov 1, 2014, funding for granisetron 1mg tablets (Granirex) became available. Other antiemetics funded in NZ include cyclizine (injections only), haloperidol, metoclopramide (tablets and injections) and prochlorperazine (tablets only).

Granisetron

Granisetron is a selective, noncompetitive 5-HT₃ receptor antagonist with a binding constant of 0.26nM, but unlike other 5-HT₃ antagonists, granisetron has negligible affinity for dopaminergic, adrenergic, benzodiazepine, histaminic, opioid and other 5-HT receptors.¹⁴⁻¹⁷ Emetogenic chemotherapies cause mucosal enterochromaffin cells to release serotonin, which stimulates 5-HT₃ receptors on vagal nerve terminals (peripherally) and the nucleus tractus solitarius (centrally). Granisetron appears to have an antagonist action on the serotonin-induced stimulation of vagal afferent activity. It is believed that serotonin has a central role in the mechanism of acute emesis but a lesser role in delayed emesis.¹⁸

Pharmacokinetics

The pharmacokinetics of granisetron differ to other 5-HT₃ antagonists such as ondansetron (Table 2).¹⁹ A unique property of granisetron among the 5-HT₃ receptor antagonists is that it is not metabolised via the cytochrome P450 2D6 pathway, meaning that patient responses are less variable due to factors such as pharmacogenomic differences.¹⁷ Granisetron has a longer mode of action than ondansetron, with ondansetron having a half-life of ~3 hours. Granisetron is also associated with longer biological activity than ondansetron, as evidenced by 2.6-fold longer inhibition of cutaneous 5-HT-induced, axon-reflex flare, with activity still present 24 hours after a single granisetron dose of 40 µg/kg (compared with ondansetron 8mg and 16mg).^{20,21} Also in contrast to ondansetron, granisetron insurmountably antagonises vagal afferent 5-HT₃ receptors, which is thought to be the underlying mechanism for its longer pharmacodynamic half-life with its plasma half-life.²²

Table 1. Antiemetic medications registered in NZ^{1,9,13,23}

Class	Agent(s)	Usage
5-HT ₃ antagonists	Granisetron	CINV/RINV Most effective combined with corticosteroid Second-line for treatment failures with other classes Oral (Granirex): indicated for prevention of acute/delayed NV associated with cytostatic therapy NZ Injections: indicated in NZ for prevention and treatment of CINV in adults; prevention of RINV in adults; prevention of CINV in children PONV Injections indicated for prevention and treatment in NZ Oral forms included in international guidelines (Table 5)
	Ondansetron	CINV/RINV Indicated in NZ for management of CINV and RINV (oral and injections) Most effective when combined with a corticosteroid Second-line therapy for treatment failures with other classes PONV Indicated in NZ for prevention
	Tropisetron	CINV/RINV Indicated in NZ for prevention (injection) PONV Indicated in NZ for treatment and prevention (injection)
	Palonosetron ^a	CINV Indicated in NZ for prevention (injection)
Antihistamines	Cyclizine	CINV/RINV Mild-to-moderate Little effect for emesis due to in highly emetogenic chemotherapy ^a PONV
Anticholinergics/antimuscarinic	Hyoscine ^c	CINV Useful as adjunctive therapy for delayed nausea or prolonged mild nausea PONV
Benzodiazepine	Lorazepam ^d	CINV Mild antiemetic activity Effective for preventing anticipatory NV
Butyrophenones	Droperidol Haloperidol ^b	CINV Useful for moderate to highly emetogenic chemotherapy ^a Optimal response as part of a multidrug regimen PONV Reduces NV
Corticosteroids	Dexamethasone ^d	CINV Important component of drug regimens – mechanism unknown Enhances efficacy of ondansetron Monotherapy appears equal to or better than 5-HT ₃ antagonists for delayed NV
Dopamine antagonists	Domperidone	CINV/RINV
NK1 inhibitors	Aprepitant ^c Fosaprepitant ^c	CINV Recently approved for highly and moderately emetogenic chemotherapy ^a PONV Aprepitant (oral) – prevention
Phenothiazines	Promethazine ^c Levopromethazine ^c	CINV Mild-to-moderate Little effect for emesis due to highly emetogenic chemotherapy ^a
	Chlorpromazine ^c Prochlorperazine ^c	PONV Retractable NV
Substituted benzamides	Metoclopramide	CINV/RINV Currently most commonly used Mild-to-moderate nausea and/or breakthrough NV PONV Controls postoperative vomiting Complicated by adverse reactions (e.g. restlessness, sedation, hypotension, diarrhoea)

a. Not funded; b. See section 'Emetic risk groups'; c. Funding restrictions apply; d. Funded under other classes/indications

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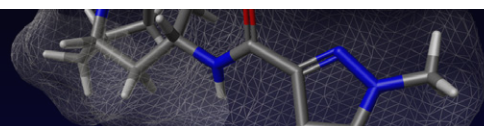


Table 2. Properties of granisetron^{15,16,24}

Molecular mass	312.41 g/mol
Route of administration	Oral (tablets)
Bioavailability	~60% – not influenced by food
Protein binding	~65%
Metabolism	Predominantly hepatic metabolism – biotransformation pathways involve <i>N</i> -demethylation and aromatic ring oxidation followed by conjugation
Elimination	12% unchanged in the urine over 48h Remainder as metabolites; 47% urinary and 34% faecal
Terminal half-life	8.74h after 1mg oral dose
Main toxicities	Constipation and headache (causally linked) Asthenia, somnolence, diarrhoea, abdominal pain, decreased appetite (main adverse events reported in clinical trials)
Main drug interactions	Potential for electrocardiographic irregularities with concomitant drugs known to prolong the QT-interval and/or are arrhythmogenic Potential for serotonin syndrome with concomitant use of agents that may affect the serotonergic neurotransmitter system
Dose adaptations	Elderly: available clinical data suggest normal adult doses are safe and effective Paediatrics: not been adequately studied Pregnancy/lactation: safety not established – not recommended unless potential benefit to mother outweighs possible risk to foetus Hepatic impairment: clearance is reduced by half (the dose response has not been determined) – dosage adjustments not required based on available data Renal impairment: available clinical data suggest dosage reduction not required

Availability

Granisetron was approved in the UK in 1991, followed by the US in 1994. A transdermal patch was approved in the US in 2008, and an application for a long-acting SC injectable formulation was lodged in 2012. Granisetron tablets, marketed as Granirex in NZ, have recently been funded for use in NZ, and they are currently indicated by Medsafe for the prevention of acute and delayed NV associated with cytostatic therapy (including RT).^{13,15} Granisetron has also been shown to be effective for PONV (refer to section 'Clinical trial data supporting the use of granisetron for NV: PONV'). Granirex film-coated tablets contain 1mg of granisetron each, and the usual dosage is 1mg twice daily for ≤7 days, with the first dose administered ≤1 hour before cytostatic therapy. Granisetron 1mg has been shown to be noninferior to 3mg, when combined with dexamethasone, for preventing acute CINV.^{25,26}

Emetic risk groups

Chemotherapeutic agents are divided into four Grunberg classes according to their emetogenic potential: high risk (≥90% of patients experience acute emesis), moderate risk (30–90%), low risk (10–30%) and minimal (<10%) (Table 3).³ Highly emetogenic chemotherapy results in vomiting in >90% of patients, but pretreatment prophylactic antiemetic use can reduce this to around 30%. However, nausea is more difficult to control. Chemotherapeutic agents associated with delayed-onset NV (>24 hours) include cisplatin, carboplatin, cyclophosphamide and doxorubicin. The maximal intensity of NV with cisplatin occurs 48–72 hours postadministration, and can persist for 6–7 days. Anticipatory NV has been reported with varying incidences of 18–57%, and nausea is more common than vomiting.

For CINV, ondansetron (oral or IV) is a commonly used antiemetic for use with chemotherapy with an emetogenic potential >30%, but combined with dexamethasone if the emetogenic potential is >60%. The newly approved NK1 inhibitors are also effective in moderately to highly emetogenic chemotherapy, including the acute, delayed and overall phases.^{27,28} Other available antiemetics are only recommended for chemotherapy with an emetogenic potential ≤30% and delayed NV.¹

RT is also classified according to emetogenic risk: i) TBI or total nodal irradiation is considered high risk; ii) upper abdomen RT and half or upper body irradiation is moderate risk; iii) cranial, craniospinal, head and neck, lower thorax region and pelvic RT are low risk; and iv) RT of the breasts or extremities is minimal risk.²⁹ Another useful assessment tool for RT emetogenic risk includes scoring both by patient factors and the emetogenic risk of the RT site.^{30,31}

Table 3. Chemotherapeutic agents with moderate to high emetogenic potential^{3,29,69}

Emetogenic risk level	Agents
High	Busulfan >10mg Doxorubicin or epirubicin plus cyclophosphamide Carmustine >250 mg/m ² Cisplatin ≥50 mg/m ² Cyclophosphamide >1500 mg/m ² Dacarbazine Doxorubicin >60 g/m ² Epirubicin >90 g/m ² Ifosfamide ≥10 g/m ² Lomustine
Moderate	Aldesleukin >12–15 million IU/m ² Azacitidine Carboplatin Carmustine ≤250 mg/m ² Cisplatin <50 mg/m ² Clofarabine Cyclophosphamide ≤1500 mg/m ² Cytarabine >200 mg/m ² Dactinomycin Daunorubicin Doxorubicin ≤60 mg/m ² Epirubicin ≤90 mg/m ² Etoposide >120 mg/m ² Idarubicin Ifosfamide <10 g/m ² Interferon alfa ≥10 million IU/m ² Irinotecan Melphalan Methotrexate ≥250 mg/m ² Oxaliplatin Temozolomide (>75 mg/m ² /day)

Evidence for the use of granisetron for NV

Acute and delayed-onset CINV

The use of antiemetic agents such as 5-HT₃ antagonists and NK1 antagonists have resulted in marked decreases in hospitalisation for chemotherapy and have nearly eliminated acute emesis.³² A number of trials and meta-analyses have demonstrated efficacy of granisetron for acute and delayed CINV.

One retrospective assessment has suggested superiority of granisetron 10 µg/kg or 1mg over ondansetron 8mg, with an 8-fold reduction in the incidence of acute CINV among 224 women who had received cyclophosphamide for breast cancer.³³ However, other RCTs have shown no difference between granisetron and ondansetron for managing CINV in patients receiving higher emetogenic chemotherapy, including a first course, a first course of single-agent chemotherapy and cisplatin-based chemotherapy, or in patients receiving conditioning therapies frequently used prior to haematopoietic stem-cell transplantation.^{34–38}

Two RCTs have shown granisetron to be superior to metoclopramide. One in patients receiving CHOP for NHL showed significantly better controls of both acute and delayed CINV and also reported a patient preference for granisetron; both agents were administered with dexamethasone on days 1–5.³⁹ The other, which also included dexamethasone therapy in each arm in patients receiving cisplatin-based therapy, reported significantly greater antiemetic control and a significantly greater delay to NV in the granisetron arm.⁴⁰ However, two trials have shown no difference between granisetron and metoclopramide, both with corticosteroids, in patients with controlled acute emesis.^{41,42} A comparison of granisetron with prochlorperazine found that granisetron was superior at 24–48 hours, but not 72 hours, in patients receiving moderately emetogenic chemotherapy.^{43,44}

A meta-analysis of seven trials comparing granisetron and tropisetron for acute CINV in patients receiving cisplatin-based therapy showed superiority of granisetron in six of the trials for complete absence of vomiting during the 24 hours after the start of chemotherapy (ORs >1), but the differences did not reach statistical significance.⁴⁵ In five trials of non-cisplatin-based regimens, an advantage of granisetron over tropisetron was seen in four of the trials, with statistical significance achieved in one. When data from all trials were pooled, granisetron was associated with a significant overall advantage over tropisetron (p=0.042), which was supported by the individual studies. The difference in response was more pronounced with non-cisplatin-based regimens than with cisplatin regimens in the ten trials in which an advantage with granisetron was seen (7.3% vs. 5.4%). A later meta-analysis of 44 randomised trials (n=12,343) by the same group showed that granisetron 2mg or 3mg was equivalent to ondansetron 24mg or 32mg, and was significantly better than tropisetron (p=0.018) for managing acute CINV.²⁵ Moreover, granisetron 3mg was found to be significantly superior to ondansetron 8mg for non-cisplatin-based therapy (p=0.015). No differences were seen between granisetron 1mg and 3mg doses.

In a trial looking specifically at delayed CINV, patients receiving new chemotherapy with doxorubicin, epirubicin, cisplatin, carboplatin or oxaliplatin were randomised to receive: i) palonosetron plus dexamethasone on day 1 with prochlorperazine on days 2–3 (n=234); ii) granisetron plus dexamethasone on day 1 with prochlorperazine on days 2–3 (n=234); iii) aprepitant plus palonosetron plus dexamethasone on day 1 with aprepitant plus dexamethasone on days 2 and 3 (n=241); or iv) palonosetron plus dexamethasone on day 1 with prochlorperazine plus dexamethasone on days 2–3 (n=235).⁴⁶ No difference was seen between granisetron and palonosetron for controlling delayed CINV, and adding dexamethasone on days 2–3 improved the effectiveness.

Antiemetic refractory patients

The antiemetic efficacy and tolerability of granisetron for CINV has also been evaluated during chemotherapy cycles in 456 patients who had failed metoclopramide, dexamethasone and ondansetron antiemetic therapy.⁴⁷ A complete response was seen in 53–60% of the patients, with antiemetic efficacy sustained throughout six successive chemotherapy cycles. Granisetron was found to be less effective with high-dose cisplatin regimens than other cytostatic regimens. An RCT in patients refractory to ondansetron plus dexamethasone following highly emetogenic chemotherapy showed there is no complete cross-resistance between 5-HT₃ antagonists.⁴⁸ The participants were randomised to receive granisetron 3mg plus dexamethasone 10mg (n=19) or continuation of ondansetron 8mg plus dexamethasone 10mg (n=21). Complete protection against CINV was seen in nine participants who switched to granisetron versus one who continued with the ondansetron regimen (p=0.005). The effectiveness of granisetron for preventing CINV in patients who have not responded to ondansetron has been possibly attributed to the lack of the cytochrome P450 2D6 involvement in granisetron's metabolism, meaning it is not subjected to genetic polymorphisms that could affect efficacy.⁴⁹

Paediatrics

An early trial in 88 children receiving ifosfamide showed significantly less NV with IV granisetron 20 µg/kg compared with IV chlorpromazine 0.3–0.5 mg/kg plus dexamethasone.⁵⁰ One trial comparing a single dose of granisetron with IV ondansetron infusions in 33 children with acute lymphoblastic leukaemia receiving moderately emetogenic chemotherapy showed no difference in clinical outcomes;⁵¹ however, another study in 60 children receiving high-dose methotrexate for acute lymphoblastic leukaemia showed that oral granisetron 1mg was more effective than oral ondansetron 4mg 30 min before surgery for preventing delayed emesis.⁵² There is also some limited evidence that granisetron is effective in children who are refractory to standard antiemetic therapy.⁵⁴

RINV, in highly and moderately emetic radiation sites

The efficacy of 5-HT₃ antagonists over placebo for preventing both emesis and nausea associated with RT (respective relative risks 0.70 [95% CI 0.57, 0.86] and 0.84 [0.73, 0.96]) has been established in a meta-analysis of nine trials, although only one trial investigated granisetron.⁵³ The efficacy of granisetron for RINV prophylaxis has been studied in patients scheduled to receive 10–30 fractions of upper abdominal RT. The trial participants were randomised to receive oral granisetron 2mg (n=134) or placebo (n=126) once daily starting 1 hour before RT.⁵⁴ Compared with placebo, granisetron was associated with a significantly longer median time to first emesis and first nausea (35 vs. 9 days and 11 vs. 1 day, respectively), and significantly greater emesis-free and nausea-free rates (57.5% vs. 42.1% and 30.6% vs. 16.7%).

A study in 30 patients receiving highly emetogenic fast-dose-rate, single-fraction TBI before bone-marrow transplantation compared granisetron with the combination of metoclopramide, dexamethasone and lorazepam for controlling RINV.⁵⁵ Compared with the combination regimen, granisetron was associated with a greater response rate at 24 hours (53% vs. 13%), significantly better control of vomiting over 24 hours and 7 days and significantly fewer doses of rescue therapy.

Oral granisetron 2mg and ondansetron 8mg administered 1 and 1.5 hours, respectively, before the same TBI regimen were compared in 90 patients scheduled for bone-marrow transplantation; a historical control group without 5-HT₃ antagonist therapy were also included in the analyses.⁵⁶ Compared with the respective ondansetron and control groups, granisetron was associated with a significantly greater proportion of participants with no episodes of emesis over 4 days (primary endpoint; 33.3% vs. 26.7% and 0%) and 24 hours (61.1% vs. 46.7% and 6.7%). Granisetron was similar to ondansetron and superior to the control group for complete emetic control over 4 days, and granisetron was also associated with fewer participants experiencing >5 episodes of emesis over 4 days than the control group, but not ondansetron recipients.

An Italian study enrolled 15 patients receiving RT 1.8–4.9Gy (for cancers) who were refractory to dopamine antagonists for RINV.⁵⁷ Treatment with oral granisetron 1–2 mg/day for 7–8 days, starting 1–2 hours before RT, resulted in immediate NV remission in 33% of the patients, and remission in 1–3 days in all patients.

PONV

The available evidence favours the effectiveness of granisetron in PONV, with most studies reporting similar or better efficacy compared with other 5-HT₃ antagonists. One RCT randomised patients undergoing laparoscopic surgery to receive oral granisetron 1mg 1 hour before surgery (n=104) or IV ondansetron 4mg after surgery (n=105), with appropriate placebos to achieve blinding.⁵⁸ These researchers found no significant difference between the groups for the incidences of postdischarge NV, rescue antiemetic requirements and quality of recovery. Similarly, no differences were seen in PONV outcomes between patients undergoing abdominal hysterectomy randomised to receive granisetron 0.1mg plus dexamethasone 8mg (n=87) compared with those randomised to receive ondansetron 4mg plus dexamethasone 8mg (n=89).⁵⁹ However, another study in 75 adults undergoing laparoscopic cholecystectomy showed granisetron was more effective than ondansetron and metoclopramide for managing PONV.⁶⁰ In this RCT, the participants received IV granisetron 3mg, ondansetron 4mg or metoclopramide 10mg administered 5–10 minutes before induction of anaesthesia. While no difference was seen for PONV scores at 0–2 hours, granisetron was found to be more effective than both the comparators at 2–6 hours, and patient satisfaction scores favoured granisetron over the other agents at 12–24 hours, but not >24 hours.

A 2013 meta-analysis of five RCTs comparing granisetron with ondansetron for PONV prevention in patients undergoing laparoscopic cholecystectomy found that although statistical significance was not reached, there was a trend for granisetron to be more effective than ondansetron in terms of early (≤12 hours) and total incidences of PONV (34.3% vs. 42.9% and 34.2% vs. 38.7%, respectively).⁶¹ Superiority of granisetron over ondansetron was also seen in another recent study in which 60 adults undergoing laparoscopic surgery were randomised to receive postsurgical IV granisetron 2mg or ondansetron 4mg.⁶² Compared with ondansetron, granisetron was associated with a significantly greater proportion of participants with no PONV and no need for rescue antiemetic therapy (86% vs. 75%), and no significant difference in the postanaesthesia recovery times.

In contrast to patients undergoing laparoscopic procedures, oral granisetron 2mg was found to be less effective than ondansetron 4mg at controlling PONV in 90 women undergoing modified radical mastectomy, but granisetron was still superior to placebo.⁶³ In another RCT, 203 women undergoing thyroidectomy were randomised to receive IV granisetron 3mg, ondansetron 4mg, tropisetron 5mg or placebo at induction of anaesthesia.⁶⁴ Compared with placebo, granisetron was the most effective of the 5-HT₃ antagonists, with reductions in the incidences of nausea at 6–18 hours and vomiting at 6–12 hours. In contrast, ondansetron reduced NV incidence at 6 hours but not at later timepoints, and the NV incidences with tropisetron did not differ significantly from those with placebo.

A comparison of four 5-HT₃ antagonists has been undertaken in a meta-analysis of 85 studies (n=15,269).⁶⁵ For PONV prevention, granisetron was found to be significantly superior to ondansetron and dolasetron (respective ORs 1.53 [95% CI 1.15, 2.00] and 1.67 [1.12, 2.38]) in preventing PONV, but when only postoperative vomiting prevention was considered, the efficacy of granisetron was not significantly better than ondansetron, tropisetron and dolasetron; the ORs were ≥1.32, but all lower limits of the confidence intervals were <1.00. This meta-analysis also confirmed that these four 5-HT₃ antagonists were all superior to placebo for preventing PONV and postoperative vomiting.

Paediatrics

There are limited data on the efficacy of granisetron for PONV in children. One study showed oral granisetron at doses 20 µg/kg and 40 µg/kg administered 20 minutes before anaesthesia induction was significantly superior to placebo in 73 children undergoing strabismus surgery.⁶⁶ The granisetron recipients had less postoperative vomiting, fewer severe vomiting episodes and were discharged earlier than placebo recipients. Postoperative vomiting outcomes did not differ significantly between the two granisetron doses.

Safety

Granisetron has generally been well tolerated in clinical trials (refer to Table 2). Compared with ondansetron, granisetron in RCTs has been associated with lower rates of: i) dizziness and vision abnormalities;³⁷ ii) headache, constipation and dizziness;⁶² and iii) headache, constipation, abdominal pain and loose bowel motions.⁶² Srivastava et al. reported lower rates of mild constipation with granisetron than with ondansetron or metoclopramide, while headache, the only other adverse event reported with granisetron, occurred at similar incidences.⁶⁰

Treatment of NV and key international guidelines

There are a number of principles that need to be considered in managing NV (see below), which is improved by adherence to clinical practice guidelines.^{1,4} As new antiemetic options continue to be developed, it is important for clinicians to stay up to date with changes in guidelines.⁴ 5-HT₃ antagonists have an important role in the management of NV, particularly in treatments with moderate-to-high emetogenic potential. They are most effective in scheduled prophylactic regimens rather than as-needed, but they are not very effective for stopping pre-existing NV and have a 'ceiling dose' above which little or no antiemetic effect is seen.¹

General Principles for managing NV (adapted from Culverwell 2008)⁶⁷

- Prophylaxis is better than treatment of vomiting
- Antiemetic regimens should be individualised for each patient
- Consider switch to as-needed therapy if no nausea for 24 hours
- Titrate dose to patient tolerance
- Combination regimens provide optimum control
- Avoid agents from same pharmacological category
- For CINV, effective prophylaxis during first chemotherapy cycle can minimise anticipatory NV
- If it's not broken, don't fix it!
- Oral administration, with adequate time for absorption before chemotherapy, is preferred for prevention of emesis

There is general consensus from international guidelines on the role of granisetron in CINV. The MASCC/ESMO (Multinational Association of Supportive Care in Cancer and European Society of Clinical Oncology; see Table 4), NCCN (National Comprehensive Cancer Network) and ASCO (American Society of Clinical Oncology) guidelines are consistent with each other and other international guidelines (e.g. UK NHS, which uses slightly different emetogenic potential classifications) with respect to 5-HT₃ antagonist use, and are the basis for the guidelines of many other organisations (e.g. Boston Medical Center).^{3,29,68–70} As many anticancer regimens include multiple chemotherapeutic agents with or without RT, the appropriate antiemetic treatment option should be that which applies to treatment with the greatest emetic risk.

Table 4. MASCC/ESMO guidelines for CINV and RINV according to emetogenic potential^{5,29}

High emetogenic potential	
CINV	RINV
Acute NV A 3-drug regimen of single doses of a 5-HT ₃ antagonist, dexamethasone and an NK1 antagonist Paediatric: 5-HT ₃ antagonist plus dexamethasone Delayed NV Patients receiving cisplatin treated with a combination of an NK1 antagonist, a 5-HT ₃ antagonist and dexamethasone to prevent acute NV: dexamethasone plus aprepitant or dexamethasone alone on days 2–3 if fosaprepitant is used on day 1 Paediatric*	5-HT ₃ antagonist (e.g. granisetron 2mg oral or 0.01 mg/kg IV) plus dexamethasone
Moderate emetogenic potential	
Acute NV Palonosetron plus dexamethasone Patients (particularly women with breast cancer) receiving an anthracycline plus cyclophosphamide: a 3-drug regimen of single doses of a 5-HT ₃ antagonist, dexamethasone and an NK1 inhibitor administered before chemotherapy Paediatric: 5-HT ₃ antagonist plus dexamethasone Delayed NV Multiple day oral dexamethasone Patients receiving anthracycline + cyclophosphamide: aprepitant or none if fosaprepitant is used on day 1 Paediatric*	5-HT ₃ antagonist with optional dexamethasone
Low emetogenic potential	
Acute NV Single antiemetic agent such as dexamethasone or a 5-HT ₃ or dopamine receptor antagonist Paediatric* Delayed NV None	Prophylactic or rescue with 5-HT ₃ antagonist
Minimal emetogenic potential	
Acute NV None in patients with no NV history Paediatric* Delayed NV None	Rescue with 5-HT ₃ or dopamine antagonist
Multiple-day cisplatin	
5-HT ₃ antagonist plus dexamethasone for acute CINV and dexamethasone for delayed CINV	N/A
Cisplatin given on days 1–5	
Consider adding an NK1 receptor antagonist starting no later than day 3	N/A
Anticipatory NV	
Treat as for acute and delayed NV and consider behavioural therapies Benzodiazepines can decrease occurrence, but efficacy decreases as chemotherapy treatment continues	N/A
*no data – treat as for adults with appropriate dose adjustments	

The recommendations for antiemetics in CINV and RINV in the Perugia Consensus Conference on Antiemetic Therapy, published in June 2009, are largely consistent with these guidelines.⁷¹ They state that 5-HT₃ antagonists combined with corticosteroids should be considered the standard of care in CINV, and that the levels of consensus and confidence are both 'high' for their use in RINV. The route of administration of these agents was also discussed in detail, with the conclusion that provided that the patient has an intact GI tract and is compliant with treatment, oral administration of granisetron is equally as efficacious as IV injections.

While guidelines sometimes recommend a specific 5-HT₃ antagonist, often the recommendation is for 'a 5-HT₃ antagonist'. In such cases, the choice of agent should consider factors such as patient age group (and evidence strength for that age group), duration of action, previous therapy, patient preference, cost and funding criteria.

The cost of Granirex under the current Pharmac schedule is \$5.98 per 50 tablets, while the cost of ondansetron for a comparable dose for use in NV (8mg) is \$6.19 per 50 tablets.¹³

Multiple day chemotherapy regimens

Managing CINV in patients receiving multiple day chemotherapy is complicated by the potential for acute and delayed NV to overlap. International guidelines recommend antiemetic therapy according to the emetic potential of the chemotherapeutic agent each day it is administered and 2 days afterward if appropriate; the option of transdermal granisetron patches (where available) is also offered to these patients rather than daily 5-HT₃ antagonist therapy.⁶⁸

PONV

The consensus guidelines for the management of PONV by the Society for Ambulatory Anesthesiology give IV granisetron 0.35–3mg administered at the end of surgery an A1 evidence rating for the prevention of PONV in adults at moderate risk.⁷² The guidelines also note that granisetron in combination with dexamethasone or cyclizine is better than monotherapy in this setting. For adults at high risk of PONV, a 5-HT₃ antagonist combined with dexamethasone or droperidol is recommended with an A1 evidence rating. Ondansetron is the preferred 5-HT₃ antagonist for preventing PONV and postoperative vomiting in children. Low-dose 5-HT₃ antagonist therapy is recommended to treat patients who develop PONV, unless it has been given prophylactically preoperatively, in which case an antiemetic from another class should be chosen.

Treatment in NZ

Although in NZ Granirex is indicated for the prevention of acute and delayed NV associated with cytostatic therapy in adults, injectable granisetron (granisetron-AFT) is indicated in adults for the treatment (as well as prevention) of CINV and the prevention of RINV and PONV, and for the treatment and prevention of CINV in children.^{15,73} Antiemetic guidelines in NZ are generally in line with international guidelines, but are often limited in their choice of agents, with ondansetron usually the 5-HT₃ antagonist of choice, likely due to it being the only oral agent from this class funded by Pharmac prior to Nov 1, 2014.^{13,67,74,75} However, the guidelines do consider alternative agents; e.g. the Canterbury DHB Oncology Department guidelines recommend considering an alternative 5-HT₃ antagonist if significant acute CINV does not respond to first-line treatment.⁶⁷ The recommended doses and costs for 5-HT₃ antagonists available in NZ are presented in table 5.

With the funding of granisetron in NZ, clinicians now have another option in their armamentarium for the management of CINV and RINV. Granisetron's role in PONV is not yet established in NZ.

Table 5. Antiemetic doses and costs for 5-HT₃ antagonists in NZ^{13,29}

Drug	Dose	Funded cost (NZ\$)
Granisetron	Oral: 1–2mg IV: 1mg or 0.01mg/kg	5.98 per 50×1mg tablet
Ondansetron	Oral: 16mg IV: 8mg or 0.15mg/kg	6.19 per 50×8mg tablet 5.51 per 50×4mg tablet
Tropisetron	Oral: 5mg IV: 5mg	8.95 per 2mL ampoule (1 mg/mL) 13.95 per 5mL ampoule (1 mg/mL)
Palonosetron	IV: 0.25mg	(not funded)

Concluding remarks and key points

Granisetron is one of several 5-HT₃ antagonists that have been proven in RCTs to be remarkably effective for the prophylactic and rescue use of NV associated with chemotherapy, radiotherapy and surgery. The 5-HT₃ receptor antagonists are the most effective drugs for managing CINV, and RCTs have shown that all 5-HT₃ antagonists are of equal efficacy. Guidelines support their routine prophylactic use for high and medium emetogenic chemotherapy regimens. RINV is usually less frequent and severe compared with chemotherapy; nevertheless, it can be a significant and distressing side effect. The prophylactic use of 5-HT₃ antagonists is recommended for patients having RT to sites where there is a moderate-to-high risk of NV and can be used effectively for rescue of NV from RT to lower risk treatment sites. Studies show that all 5-HT₃ antagonists are effective when used prophylactically or for the rescue of PONV. Granisetron is well tolerated; the most frequently reported adverse event is headache, with constipation, dizziness, asthenia and somnolence being less commonly reported. Several studies suggest that some of these side effects are less common compared with the other 5-HT₃ antagonists. The funding of Granirex means that clinicians now have access to another option for the management of CINV and RINV.



Research Review Product Review

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