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Granisetron: a review of pharmacokinetics and clinical experience in chemotherapy induced - nausea and vomiting

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Abstract

Introduction:

Chemotherapy induced nausea and vomiting (CINV) are major side effects of chemotherapy and a great burden to patients’ quality of life. Serotonin and substance P are the major neurotransmitters involved in the pathophysiology of CINV, but in spite of new antiemetics no completely effective regime exists for its prevention or treatment.

Areas covered:

In this review the authors provide a detailed description of granisetron’s chemistry pharmacokinetics, pharmacodynamics, toxicity and a brief review of clinical trials involving granisetron and the management of CINV. We searched reviews, meta-analysis and randomized controlled trials (Medline, Embase and article reference lists).

Expert opinion:

According to current literature, granisetron 2 mg orally or 0,01mg/kg (1 mg) intravenously per day, co-administered with dexamethasone and NK-1 antagonists is the recommended regime for highly emetogenic chemotherapy. In the future the role of transdermal and subcutaneous formulations against delayed CINV will be clarified and probably enhance patients’ convenience.

Keywords: Granisetron, Chemotherapy induced nausea and vomiting, CINV, 5-HT3 antagonists, pharmacokinetics, pharmacodynamics
1. Introduction to CINV

Nausea and vomiting are common side effects of chemotherapy which hamper the quality of life of patients with cancer and can even lead to dose reduction or refuse of treatment [1,2]. The incidence of CINV depends on the emetogenic potential of the chemotherapeutic agent and patients’ risk factors (young age, female gender, history of low alcohol intake, history of emesis during pregnancy, impaired quality of life, previous chemotherapy) [1,2]. Despite the discovery of new antiemetic agents and guideline implementation, complete prevention of CINV is achieved in 70-84% of patients [3,4].

2. Pathophysiology of CINV

The pathophysiology of CINV is complex and involves the interaction of peripheral and central structures disseminated throughout the medulla oblongata [5]. Acute CINV occurs 0-24 hours after chemotherapy, mainly caused by serotonin release by enterochromaffin cells. Serotonin activates 5-hydroxyl tryptamine type-3 (5-HT3) receptors in the vagal afferents which transmit the stimulus to the brain. Delayed CINV (24-120h after chemotherapy) is largely caused by the activation of neurokinin-1 (NK-1) receptors located in nucleus tractus solitarius. Substance P is the main neurotransmitter acting on NK-1 receptors. Studies suggest that there is a synergistic interaction between 5-HT3 and NK-1 receptors in controlling CINV; activation of one receptor augments the responses of the other receptor system [1,6]. Recent guidelines recommend the combined use of 5-HT3, NK-1 antagonists and dexamethasone for the management of high risk patients [1,2]. Glucocorticoids are considered to exert these effects though several mechanisms including their anti-inflammatory action, inhibition of 5-HT expression, direct action on nucleus tractus solitarius and regulation of the hypothalamic-pituitary-adrenal axis. Glucocorticoids are effective in preventing but not for treating established nausea and vomiting [7].

Granisetron is a first generation 5-HT3 antagonist broadly used for the prevention of CINV. The purpose of this report is to review the role of granisetron for CINV.

3. Introduction to granisetron

Granisetron hydrochloride (1-Methyl-N-(endo-9-Methyl-9-Azabicyclo(3.3.1)non-3-yl)-1H-Indazole-3-Carboxamide) is an indazole with empirical formula C18H24N4O•HCl
and molecular weight of 348.87. It is a white to off-white solid substance, readily soluble in water and normal saline at 20°C. Granisetron is a basic lipophilic drug, moderately bound with proteins (65%) [8], and is available for intravenous administration, as a tablet, oral solution and transdermal system, and recently an extended release injection has been approved by FDA [9].

4. Pharmacodynamics
Granisetron is a highly selective non-competitive antagonist of 5-HT3 receptors which exerts minimal effect on other receptors [10].

Studies in guinea-pig isolated ileum and other models of 5-HT3 receptor activity (rabbit isolated heart, Bezold-Jarisch reflex in anaesthetized rats) demonstrated potent antagonism by granisetron, while radioligand binding studies on rat brain membranes showed that it had little or no affinity for 5-HT1A, 5-HT1B, 5-HT2, 5-HT1C, α1- and α2-adrenergic, dopamine D1 and D2, histamine H1, benzodiazepine, β-adrenergic, and opioid receptors [11,12,13]. The pKi of granisetron was 8.42, and it was calculated that the selectivity of granisetron binding at 5-HT3 over other receptors is greater than 1000:1 [13].

It has also been proposed that granisetron may act directly on enterochromaffin cells, since it reduces the release of endogenous 5-HT in isolated guinea-pig small intestine [14], and inhibits the cisplatin induced release of 5-HT from the isolated ileum of the ferret [15]. Similar effects have not been observed in humans and it seems that it acts solely through 5-HT3 receptors blockade on vagal afferents [16].

5. Pharmacokinetics and metabolism
All pharmacokinetic studies on granisetron showed a great inter-subject variability of its pharmacokinetic parameters, regardless of formulation administered or population studied. In healthy volunteers after intravenous administration, plasma concentration of granisetron displays multi-phasic decline, whereas it becomes log-linear after several hours. The rapid initial decline of plasma concentration implies extensive tissue uptake, which is also depicted on a relatively high apparent volume of distribution ranging from 2.4-3.5L/Kg. Clearance is mainly non-renal and ranges between 37-49.9L/h (approximately 0.6L/kg/h). Approximately 12% of the drug is excreted unchanged in the urine. Terminal phase t_{1/2} ranges from 4.2-6.1h [17]. Elderly patients (age>65 years)
display a higher volume of distribution (approximately 4 vs 3L/kg) which probably results from an increased fat: lean mass ratio. Total plasma clearance is 45% lower, a result of age-related reduction in oxidative metabolism [0.17-1.06 (mean 0.44)L/kg/h] and elimination t₁/₂ of granisetron is approximately 7.7h. In volunteers aged>65 years AUC after a 40mcg/kg intravenous dose of granisetron was 115±52.2 versus 89.7±58.8ng/ml/h observed in the younger group [8]. In adult patients receiving chemotherapy, granisetron clearance is decreased compared to healthy adults (0.376L/kg/h). As a result, terminal phase elimination t₁/₂ was longer (9-12h) [18,19]. Notably, a definite relationship between anti-emetic efficacy and peak plasma concentration or AUC time curves could not be demonstrated in studies assessing the pharmacokinetics and the efficacy of the drug [18,20]. Although AUC values were higher in responding patients, the difference was not statistically significant and there was no defined plasma concentration threshold for the drug's anti-emetic effect in patients who responded to treatment [20].

To our knowledge there are no pharmacokinetic studies in healthy children. Pharmacokinetic data on pediatric cancer patients are scarce and, again, display significant variability between subjects. For example, in a study of 7 children given a dose of 1-3mg granisetron for the management of CINV, Cmax, elimination t₁/₂, AUC, Vd, and CL ranged 31.8—104.2mg/L, 7.8-66.8 h, 315.4-1006.1 mcg/L/ h, 1.01-7.66 L/kg, and 0.051-0.253 L/kg/h respectively [19]. In another study in children with cancer, the volume of distribution and total plasma clearance depended on the age of the enrolled children [21]. After a single dose of 40mcg/kg, clearance was 0.193±0.146L/kg/h in the age group 2-6, whereas in children 7-11 and 12-16 years old it was 0.352±0.341 and 0.360±0.271L/kg/h respectively. The same applied for Vd which increased with increasing age (19.8L in the age group 2-6 years, 60.8L in 7-11 year-old, 71.3 in 12-16 year-old). However after normalization for bodyweight the relationship between age and both Vd and CL was no longer significant. No differences were observed on maximum plasma concentration (45.2-59.9ng/ml) and t₁/₂ (5.82-8.92h) among the three age groups. Most importantly, no apparent relationship was found between the lack of efficacy and Cmax or AUC in patients who failed to respond to granisetron [21].
Recently it has been suggested that the efficacy of pharmacological action of transmitter receptor antagonists is dependent on the rate of occupancy of the target receptor which, in the case of 5-HT3 antagonists, should be 67–97% at therapeutically effective doses [22]. In patients receiving cisplatin, Yamada et al were able to demonstrate a positive relationship between average receptor occupancy and complete vomiting inhibition rate, whereas no significant relationship between antiemetic efficacy and standard dose or plasma unbound drug concentrations was observed [23]. The time course of 5-HT3 receptor occupancy in adult patients receiving 2mg oral granisetron is 65–95% during 24 hours after treatment [24]. Since the receptor occupancy required to demonstrate antagonistic effect is reported to be in general 60-70%, granisetron at this dosage seems to be effective for prevention of acute (0-24 hours) CINV.

Absorption of granisetron after oral administration is complete but bioavailability is about 60% due to first pass metabolism. Granisetron is detectable in plasma after 1h, and maximal mean concentration is reached 2h after administration. Oral administration of the drug results in significant heterogeneity in systemic availability which appears to be related to smoking habits of healthy volunteers [25].

In an effort to increase compliance with antiemetic treatment and provide control of CINV with a lower maximum plasma concentration of the drug, a prolonged delivery transdermal system of granisetron (Granisetron Transdermal System, GDS) has been developed [26, 27]. It exists as a 52cm² patch containing 34.3mg of granisetron delivering 3.1mg per 24h for up to 7 days [26,27]. Maximal concentration is reached 48–56h post-application [26,28] and mean plasma concentration remains relatively stable for 96h. $C_{avg}$ is 2.23ng/ml, $AUC_{0-\infty}$ is 420ng.h/ml and the apparent elimination $t_{1/2}$ is 36h [26,27]. Again, a high inter-subject variability on pharmacokinetic parameters is observed [26]. The 52cm² patch provides similar exposure to granisetron to a 2mg oral dose. Clearance is not affected by age, gender, weight, or renal function however a high inter-subject variability in systemic exposure is observed [26].

Granisetron is also available as an extended release formulation for subcutaneous injection (AFP530). Each pre-filled syringe contains 10mg of granisetron in 0.4ml
incorporated in an extended-release polymer formulation, and it can be administered every 7 days in patients with normal renal function [29]. In healthy volunteers maximum drug concentration is achieved in 11-12h, Cmax ranged from 9.8-10.8 (±4.6ng/ml) and AUC\text{inf} ranged from 680-720 (±364ng.h/mL) [30]. In patients peak plasma granisetron concentrations were delayed compared to healthy subjects [29]. Two pharmacokinetic phase II trials on cancer patients showed that maximum drug concentration with this formulation was achieved in 28-31h. Cmax was 17.81ng/ml and AUC\text{0-24} and AUC\text{0-168} ranged from 256-315 to 1,385-996ng.h/ml respectively. Elimination t\text{1/2} ranged from 26.16-28.8h and apparent clearance was 27.5ml/h [30]. The subcutaneous formulation may be more effective than other 5-HT3 agents in the delayed phase because of the long half-life and therapeutic levels not relying on compliance and adherence to instructions. The precautions that should be taken in patients with impaired renal function have to do with the elimination of the breakdown products of the polymer vehicle contained in the formulation, which can be prolonged in renal dysfunction, and not with granisetron per se [29].

As previously mentioned, approximately 12% of granisetron is excreted unchanged in urine and the remainder is metabolized in the liver. 7-hydroxyl and 9-dimethyl granisetron are the major byproducts of metabolism. The enzymes responsible for metabolism are members of the CYP3A family. CYP3A3/4 are responsible for 9-desmethylation and possibly CYP3A5 for 7-hydroxylation. 7-hydroxylation is the major route of metabolism and 9-desmethylgranisetron is observed only as a minor metabolite. The high variations of granisetron clearance seen in all pharmacokinetic studies of the drug may be explained by the variable levels of CYP3A5 [31,32]. A study of Nakamura et al implicates a contribution of CYP1A1 to the metabolism of the drug as well [33].

The mainly hepatic metabolism of granisetron raises concerns regarding its administration to patients with liver insufficiency. In a study comparing pharmacokinetics, efficacy and tolerability of granisetron in patients with neoplastic involvement of the liver to patients without liver involvement after a 40mcg/kg dose, no significant differences in clearance or efficacy were observed. Consequently dose adjustment is not required for patients with liver insufficiency [34]. Similarly, the limited
renal excretion of the drug does not require dose adjustment in patients with severe renal impairment who receive a single 40mcg/kg dose.

6. Pharmacogenomics

Granisetron is metabolized by members of the CYP3A family of enzymes, therefore its efficacy is considered not to be affected by potential genetic polymorphism [35]. However in a study in Malaysian population, granisetron was found to be significantly ineffective in Chinese women with breast cancer, compared to women of Malay or Indian origin. These results were attributed to racial genetic polymorphism of CYP3A4 of the Malaysian population, but should be carefully interpreted since genotyping of the enrolled patients was not performed and the conclusion of the study relied on previous reports on polymorphism of CYP3A4 [36]. In a study in pregnant women, differences in systemic clearance and exposure of granisetron were attributed to polymorphisms in CYP3A5 and CYP1A1. Again, these results should be interpreted cautiously, since the studied population consisted of only 16 women [37].

Recently, the effects of genetic polymorphism of ABCB1 drug transporter on resistance to 5-HT3 receptor antagonists have gained much attention. This adenosine triphosphate–binding cassette subfamily 1 transporter, also known as P-glycoprotein, is expressed in organs involved in drug absorption and elimination, and it is considered to affect brain penetration of drugs. There are studies showing that cancer patients with ABCB1 2677TT and 3435TT genotypes responded better to granisetron or palonosetron [38,39,40].

7. Safety profile

The commonest side effects of granisetron are headache (10-15%), constipation (2-4%), somnolence (2.5-5%), diarrhea (0.6-2%) and dizziness (0.5-3.2%). Constipation is dose dependent. In healthy volunteers it was first encountered with a dose of 80mcg/kg, it was noted about 24h after administration, and it resolved spontaneously after 48-72h [8]. The most worrisome adverse effect of 5-HT3 antagonists is QT prolongation. None of the studies examining the cardiac effects of granisetron revealed significant changes of the QT interval in healthy adult volunteers [28], or adult cancer patients [41-45]. On the other
hand, there is evidence suggesting a possible genetic predisposition to QT prolongation after the administration of 5-HT3 antagonists. A study on surgical patients receiving granisetron 1 mg or dolasetron 12.5 mg for postoperative nausea and vomiting, demonstrated that individuals homozygous or heterozygous for the major SNP rs10494366 allele are at increased risk of developing significant QTc interval prolongation following the administration of these agents, compared to homozygous carriers of the minor allele [46]. In the literature, there is also a case report of a surgical patient who suffered of intraoperative cardiac arrest following the administration of 1 mg granisetron [47]. In children the data are conflicting. In a study of 22 children with leukemia, 40mcg/kg of granisetron resulted in a statistically significant decrease of mean heart rate at 1 and 3h, and significant prolongation of mean QT and QTc dispersions 1h post-infusion, whereas ondansetron at the equivalent dose of 0.1mg/kg did not have any significant effects [48]. In 28 children with cancer granisetron administration resulted in a significant shortening of the PR interval and QRS complex duration 90 min and 24h, while granisetron infusion caused a significant prolongation of the QTc a interval at 90 min [49]. In a recent study of 16 pediatric patients, granisetron at a dose of 40mcg/kg resulted in a statistically significant decrease in heart rate 1h post infusion which returned to baseline values within 24h, while at a 10mcg/kg dose only borderline bradycardia was detected. The 10mcg/kg dose also resulted in PR interval shortening that was not observed at the 40 mcg/kg dose. QTc interval and dispersion were not affected [50]. The findings of the last three studies were considered minor by the authors and unlikely to lead to arrhythmias. Nevertheless it is suggested that granisetron should be administered with caution in patients under treatment with drugs known to prolong QT interval.

The drug crosses the placenta in a dose depended manner. A recent study, using an ex vivo placenta perfusion model, tested trans-placental passage of granisetron at two different concentrations, mimicking intravenous and transdermal administration. The 50ng/mL concentration, representing intravenous administration, resulted in 0% up to 25% of total drug crossing the placenta, whereas no detectable passage could be demonstrated with the lower concentration of 5 ng/mL (mimicking transdermal patch delivery) [51]. There are no published data regarding birth defects and granisetron use
during pregnancy. Experimental data from primary cells isolated from human fetal organs (16–19 weeks gestational age) and treated with 3ng/mL or 30ng/mL of granisetron, showed up to 10% apoptosis in cardiac tissue at high concentration whereas no detectable toxicity was found at the 3ng/mL concentration [52]. The clinical significance of these results needs to be confirmed with further studies.

8. **Dosing routes**

Oral granisetron should be administered within 1h before the start of therapy. The recommended dose is 2 mg or 1 mg twice daily for adults [2,53] and 20-40mcg/kg/dose twice daily for children [54].

The intravenous dose for adults and children is 10mcg/kg or 1mg and 40mcg/kg respectively.

Transdermal granisetron provides a dosage of 3.1mg/day. The patch should be applied 24-48h before chemotherapy and can be worn for up to 7 days. It should be kept for at least 24h after chemotherapy completion [27].

The recommended dosage of subcutaneous granisetron is 10mg administered as a single injection at least 30min before the start of emetogenic chemotherapy and therapeutic levels were maintained for up to 140 h. It can be repeated after 7 days but its use is not recommended for more than 6 months [29].

9. **Phase II Clinical Trials**

The first trials in cancer patients were conducted in the late ‘80s, and clearly demonstrated the efficacy of granisetron against CINV [18,20,55]. Granisetron was tested at different doses, ranging from 2-160mcg/kg. All studies demonstrated that a dose 10-40mcg/kg is effective and safe. In patients subjected to highly emetogenic chemotherapy (HEC) the complete response rate, ranged from 63-70% and failures from 3-5% [18,20,55-60].

10. **Phase III Clinical trials**
In the early ‘90s, the first trials comparing granisetron to the standard therapy of that time clearly showed that granisetron had comparable efficacy with high dose metoclopramide plus dexamethasone or high dose metoclopramide plus dexamethasone plus diphenhydramine, and was far better than the combination of chlorpromazine plus dexamethasone. More importantly, extrapyramidal reactions, commonly seen after high dose of metoclopramide were never encountered with granisetron [61-63].

Granisetron is considered to have similar efficacy compared to other first generation 5-HT3 antagonists (tropisetron, ondansetron and dolasetron) although there is evidence for a small but clinically relevant superiority over tropisetron [64-73]. It is suggested that the selection of one drug over the other to be based on economic criteria.

Regarding the management of delayed CINV, the efficacy of oral or intravenous granisetron is limited. This effect is somehow expected, since plasma concentration of 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) increases with a peak at 4-6 h and returns to the basal level within 24 h after injection in patients receiving cisplatin at >50mg/m² suggesting that delayed CINV is not dependent on serotonin release [16]. In 1995 the Italian group for antiemetic research published a study examining the effects of the addition of 4mg dexamethasone to 3mg of granisetron in patients receiving moderately emetogenic chemotherapy (MEC) [74]. They found that the effects of CINV of dexamethasone and granisetron were comparable (complete protection from acute CINV: 49.3% and 43.1% respectively) but significantly higher in the combination group (70.4%). The same study revealed the role of dexamethasone and the importance of combining granisetron with dexamethasone for the prevention of delayed CINV since dexamethasone alone or the combination of the two drugs were found to be significantly more effective (complete protection from CINV for the days 2-5: 54.5% and 51.1%, respectively) than granisetron alone (34.3%) [74].

The results of studies comparing granisetron to palonosetron, a second generation 5-HT3 antagonist, are inconsistent. In study of 1143 patients receiving HEC, the administration of 0.75 mg palonosetron plus dexamethasone, resulted in complete response in 51.5% of patients 24-120h post chemotherapy, compared to 44.5% of patients who received granisetron 40mcg/kg plus dexamethasone. The effects of the two drugs in acute CINV
were comparable [75]. A subsequent study had similar results [76], but it should be mentioned that in both studies palonosetron dose was 0.75 mg, 3 times the dose currently recommended [2]. Other studies failed to reveal a superiority of palonosetron over granisetron [77,78]. Meta-analysis and systematic reviews are also inconsistent; Schwartzberg et al found that complete response rate was significantly higher for palonosetron versus older 5-HT3 antagonists in the delayed (57 vs 45 %, P<0.0001) and overall periods (51 vs 40 %, P<0.0001) [79], whereas the results of Tricco AC et al [80] do not support this conclusion. On the other hand Brodre et al supports that management of CINV with palonosetron saves costs [81]. According to the latest guidelines of the American Society of Clinical Oncology (ASCO), for HEC there is no evidence of the superiority of one 5-HT3 antagonist over the other therefore drug choice should be cost – driven. However, the preferred 5-HT3 receptor antagonist for patients who receive MEC regimens is palonosetron combined with a corticosteroid [82].

Currently phase III trials focus on the efficacy of transdermal (GDS) and extended release formulations of granisetron.

GDS has been tested for non-inferiority against oral granisetron in a study of 582 patients who received MEC and HEC; GDS provided similar prophylaxis to oral granisetron against acute and delayed CINV [83]. Similar data were provided by subsequent studies testing GDS against different regimes of oral and intravenous granisetron [84,85].

AFP530, the extended release formulation of granisetron for subcutaneous injection 250 and 500mg (5 and 10mg of granisetron respectively) have been found to be non-inferior to 0.25mg of palonosetron for the management of early and delayed emesis, in patients receiving MEC and HEC [86,87]. Furthermore, the Magic trial, the only phase III trial comparing modern era triple therapy, showed that the combination of AFP530 500mg with dexamethasone and fosaprepitant was superior compared to the combination of ondansetron 0,15mg/kg, dexamethasone and fosaprepitant in delayed CINV: Complete response was achieved in 64.7% of patients in AFP group, compared to 56.6% in the ondansetron group (p=0.014) [88]. Subcutaneous granisetron is the only FDA approved 5-HT3 antagonist for the management of delayed CINV due to HEC.
11. Postmarketing surveillance

To our knowledge the only post-marketing surveillance trial on granisetron was designed to examine the efficacy of the transdermal patch compared to palonosetron [89]. The study included 182 patients who received MEC, and who were randomized to receive at the first cycle of chemotherapy either GTS patch 10 mg or palonosetron 0.25 mg iv. Patients in both groups also received dexamethasone 10 mg. During the second cycle of chemotherapy the group initially assigned to receive GTS patch, changed to palonosetron and vice versa. Transdermal granisetron displayed similar efficacy to palonosetron regarding the prevention of acute and delayed emesis, in patients receiving MEC, while patient’s satisfaction with GTDS was higher.

12. Drug - drug interaction

There aren’t many reports on the interaction of granisetron with other drugs. A general recommendation is to avoid its concomitant use with drugs known to prolong the QT interval, as a general precaution for 5-HT3 antagonists but we couldn’t find relevant data. In an in vitro study it was found that ketoconazole inhibits the metabolism of granisetron, but no relevant in vivo data are available [31]. Furthermore, in vitro data support that granisetron does not affect hepatic enzymes activity. There is a theoretical interaction of the metabolism of granisetron with other drugs that either inhibit or induce CYP3A enzymes [90]. In healthy adults it was found that cimetidine does not affect the pharmacokinetics of granisetron [91]. The same applies to aprepitant [92] and casopitant [93].

The interaction of granisetron with SSRI’s is clinically relevant; apart from the risk of serotonin syndrome for which a few reports exist [53,94,95], co-administration with SSRI’s has been found to decrease the antiemetic efficacy of granisetron [96].

13. Conclusion

Granisetron is available for oral, intravenous, subcutaneous and transdermal use. Optimal intravenous dose is 1mg administered 30min before chemotherapy. Current recommendations support its concomitant use with dexamethasone and NK-1 antagonists for the management of HEC. Side effects are generally mild and include headache,
constipation and dizziness. It should be used with caution in patients under treatment with drugs known to prolong QT interval.

14. Expert opinion

Granisetron is a first generation 5-HT3 receptor antagonist widely used for CINV. The recommended oral dose is 2mg/day in adults. It has a long history of use for CINV and its effectiveness in the first 24 hours post therapy has been proved by many studies. Granisetron’s efficacy is similar to other first generation antagonists, but data comparing its effects with dolasetron are inconsistent, most probably favoring dolasetron for delayed CINV in patients receiving MEC. Granisetron is highly selective for 5-HT3 receptors a property which renders the drug one of the safest 5-HT3 antagonists. It has a very good safety profile, and it is the 5-HT3 antagonist with the fewer effects on QT interval. The clinician has to be careful with the interaction of granisetron with SSRIs, a combination which decreases the efficacy of the drug and may rarely cause serotonin syndrome. From a pharmacokinetic point of view, granisetron displays a great variability in all pharmacokinetic parameters and most importantly, there is not apparent relationship between efficacy and plasma concentration. However, its efficacy is consistent with receptor occupancy. Most studies suggest that it is not affected by genetic polymorphism of P450 enzymes but this may depend on the racial origin of the studied population. Furthermore polymorphisms of drug transporters influence its effectiveness. Since genotyping is for the moment rather expensive, the clinician should keep in mind that non-responders may have a genotype that does not favor granisetron’s penetration through membranes.

The efficacy of oral and intravenous granisetron, and every other first generation antagonist, for the management of delayed CINV is limited. Nowadays, a transdermal patch and an extended release subcutaneous injection exist, with promising effects regarding its efficacy on delayed CINV. As previously mentioned, the application of the GDS or the subcutaneous formulation provides prolonged release of the drug. Therefore therapeutic levels are maintained for longer period of time. The phase IV trial by Seol et al found that transdermal granisetron was not inferior compared to palonosetron while patients’ satisfaction was higher in the GDS group. Similarly, the Magic trial showed that
subcutaneous granisetron in triple therapy was superior to ondansetron in triple therapy for delayed CINV for HEC and subcutaneous granisetron is now approved by FDA for delayed CINV. Future studies will help us clarify better the role of these two formulations in terms of cost-effectiveness. Ongoing research may also lead to the development of transdermal and subcutaneous formulations for children.

The pathophysiology of CINV is complex, thus a combination of antiemetics is the most appropriate way to treat it. Granisetron should be co-administered with dexamethasone or NK-1 antagonists to optimally treat delayed CINV, especially in patients subjected to highly emetogenic therapy.

The incidence of CINV depends on the emetogenic potential of the chemotherapeutic agent and patients’ risk factors (young age, female gender, history of low alcohol intake, history of emesis during pregnancy, impaired quality of life, previous chemotherapy). The clinician has to take into account all these factors in order to tailor drug choice according to patients’ needs while the cost of therapy should also be taken into account.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
References

Papers of special note have been highlighted as: * of interest ** of considerable interest

   • a thorough review on CINV pathophysiology and guidelines for management

   • guidelines for CINV management


   • thorough review on CINV pathophysiology

   • a thorough review of the antiemetic properties of corticosteroids


   • a very precise report of the target site occupancy theory


   • an excellent report of safety issues of antiemetic medications


- the latest guidelines for CINV issued by ASCO


86. Boccia R, O'Boyle E, Cooper W. Randomized phase III trial of APF530 versus palonosetron in the prevention of chemotherapy-induced nausea and vomiting in a subset of patients with breast cancer receiving moderately or highly emetogenic chemotherapy. BMC Cancer 2016; 16: 166.


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<tr>
<th>Box 1. Drug summary</th>
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<tr>
<td><strong>Drug name</strong></td>
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<td><strong>Phase</strong></td>
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<td><strong>Indication</strong></td>
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<td><strong>Mechanism of action</strong></td>
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<td><strong>Chemical structure</strong></td>
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<td><strong>Pivotal trials</strong></td>
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Table 1. Summary of pharmacokinetic parameters of granisetron.

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<th>AUC</th>
<th>Cmax</th>
<th>Tmax</th>
<th>CL</th>
<th>Elimination t_{1/2}</th>
<th>V_d</th>
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<tr>
<td><strong>Intravenous Administration</strong></td>
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<tr>
<td>Healthy Adults</td>
<td>89.7±58.8 ng/ml/h</td>
<td>11.2-182 (mean 64.3) ng/ml</td>
<td>0.6 L/Kg/h (0.20-2.56)</td>
<td>4.2-6.1 h (0.88-15.2)</td>
<td>2.4-3.5 L/Kg (1.68-6.13)</td>
<td></td>
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<tr>
<td>Healthy Elders (age&gt;65y years)</td>
<td>115±52.2 ng/ml/h</td>
<td>14.6-153 (mean 57.0) ng/ml</td>
<td>0.17-1.06 (90.17-1.06) L/Kg/h</td>
<td>7.7 h (2.65-17.7)</td>
<td>4 L/Kg (1.75-7.01) (mean 3.97)</td>
<td></td>
</tr>
<tr>
<td>Adult Cancer Patients</td>
<td>18.0-176 (mean 63.8) ng/ml</td>
<td>31.8-104.2 mg/L</td>
<td>0.376 (0.14 – 1.54) L/Kg/h</td>
<td>9-12 h (0.9-31)</td>
<td>0.85-10.4 (mean 3.07) L/Kg</td>
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</tr>
<tr>
<td><strong>Pediatric Patients</strong></td>
<td></td>
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<tr>
<td>Dose 1-3 mg</td>
<td>315.4-1006.1 mcg/L/h</td>
<td>45.2-59.9 ng/ml</td>
<td>0.193±0.1 46 L/Kg/h</td>
<td>5.82-8.92 h</td>
<td>19.8 L</td>
<td></td>
</tr>
<tr>
<td>2-6 years old not reported</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7-11 years old not reported</td>
<td>&gt;&gt;</td>
<td></td>
<td></td>
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<tr>
<td>12-16 years old not reported</td>
<td>&gt;&gt;</td>
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<tr>
<td><strong>Oral Administration</strong></td>
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</tr>
<tr>
<td>Healthy Adults</td>
<td>3.63</td>
<td>5.99</td>
<td>0.41</td>
<td>0.52</td>
<td>Not Determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>Cancer Patients</td>
<td>[0.27 to 9.14]</td>
<td>[0.63 to 30.9]</td>
<td>[0.11 - 24.6]</td>
<td>[0.09 - 7.37]</td>
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<tr>
<td><strong>Transdermal System - GDS</strong></td>
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<tr>
<td>Healthy Adults</td>
<td>AUC_{inf} 680-720±364</td>
<td>48-56 h</td>
<td>C_{avg}2.23 ng/ml</td>
<td>36 h</td>
<td>Not determined</td>
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<tr>
<td>Ext. release subcutaneous injection – AFP530</td>
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</tr>
<tr>
<td>Healthy Adults</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Patients</td>
<td>AUC&lt;sub&gt;0-168h&lt;/sub&gt; 1385-996 ng.h/ml</td>
<td>17.81 ng/ml</td>
<td>28-31 h</td>
<td>27.5 ml/h</td>
<td>26.16-28.8 h</td>
<td>Not determined</td>
</tr>
</tbody>
</table>
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