ISSN: 2692-5370
Anaesthesia & Surgery Open Access Journal
DOI: 10.33552/ASOAJ.2023.04.000587
Iris Publishers

Review Article

Granisetron: An Overview of Its Pharmacology, Clinical Efficacy, and Safety

Yaaqoob Alhammadi*[1], Girishkumar Modi[2], Muhammad Taieb Hakmee[3] and Christoleenan Christudas Leela[4]

[1]*Anesthesiologist, Intensivist, PhD Tawam Hospital, UAE*
[2]*Anesthesiologist, FLTA, Tawam Hospital, UAE*
[3]*Anesthesiologist, Tawam Hospital, UAE*
[4]*Anesthesiologist, FCAI, Tawam Hospital, UAE*

***Corresponding author:** Yaaqoob Alhammadi, Anesthesiologist, Intensivist, PhD Tawam Hospital, UAE.

Received Date: September 06, 2023

Published Date: September 14, 2023

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is still one of the most distressing and common side effects of chemotherapy for cancer patients [1]. Antiemetic agents, of which Granisetron is an essential and highly effective choice, have been widely used to mitigate these adverse effects. Granisetron is a medication in the class of drugs known as serotonin 5-HT3 receptor antagonists. It is used to prevent or treat nausea and vomiting caused by a variety of factors, including chemotherapy, radiation therapy, post-operative nausea, and motion sickness.

Abbreviations: CINV: Chemotherapy-induced nausea and vomiting; RINV: Radiation-Induced Nausea and Vomiting; PONV: Post-Operative Nausea and Vomiting

Pharmacology

Granisetron hydrochloride is available in a variety of formulations, including oral tablets, sublingual tablets, and intravenous (IV) injections, allowing for patient-specific administration. The IV form is especially useful for patients who are unable to swallow due to chemotherapy or other medical conditions.

In terms of pharmacokinetics, cancer patients who took 1mg of granisetron twice a day for 7 days had a peak plasma concentration of 5.99ng/mL [range: 0.63 to 30.9ng/mL]. The terminal phase plasma half-life was not measured when the drug was given by mouth, but it was measured after a single intravenous dose of 40 mcg/kg. It was 8.95 hours. When cancer patients took 1 mg twice a day for 7 days, the total clearance of granisetron was found to be 0.52 L/h/kg [range: 0.09 to 7.37 L/h/kg] [2, 3].

The oral bioavailability of granisetron is reduced to about 65% due to first-pass metabolism, and 65% of the drug is bound to plasma proteins. The metabolism of granisetron includes N-demethylation, aromatic ring oxidation, and conjugation. The primary mechanism of clearance is hepatic metabolism, and after 48 hours, 11% of orally administered doses are eliminated unchanged in the urine. The remainder of the dose is eliminated as metabolites; 48% is eliminated in the urine, and 38% is eliminated in the feces [4].

In terms of pharmacodynamics, granisetron stops serotonin from stimulating the vagal and splanchnic nerve receptors that lead to the medullary vomiting center as well as the 5-HT3 receptors in the area postrema [5]. This triggers the vomiting reflex and causes nausea and vomiting. Granisetron is in a class of medications called 5-HT3 receptor antagonists, which work by blocking serotonin, a natural substance in the body that causes nausea and vomiting. It blocks the action of chemicals in the body that can trigger nausea and vomiting. Granisetron specifically inhibits type 3 (5-HT3) serotonergic receptors [6]. Other receptors, such as Serotonin receptor (5-HT1, 5-HT1A, 5-HT1B/C, or 5-HT2), alpha1-, alpha2-, or beta-adrenoreceptors, dopamine D2 receptors, histamine H1 re-

ceptors, picrotoxin receptors, or opioid receptors, have little to no affinity for granisetron.

The serotonin 5-HT3 receptors are found in the peripheral vagus nerve terminals and in the central chemoreceptor trigger zone of the area postrema [7]. The temporal relationship between emetogenic drugs' emetogenic action and serotonin release, as well as the efficacy of antiemetic agents, suggests that chemotherapeutic agents release serotonin from enterochromaffin cells in the small intestine by causing GI tract degeneration. The serotonin then stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT3 receptors in the area postrema, causing nausea and vomiting [8].

Mechanism of action of granisetron

Granisetron is a potent and selective antagonist of the serotonin 5-HT3 receptor, which is a ligand-gated ion channel that mediates fast synaptic transmission in the central and peripheral nervous systems. Granisetron binds to the 5-HT3 receptor with high affinity and blocks the influx of sodium and calcium ions that occurs upon serotonin binding. This prevents the depolarization of the postsynaptic neuron and the subsequent release of neurotransmitters such as acetylcholine, substance P, or dopamine. By inhibiting the 5-HT3 receptor, granisetron reduces the activation of the vomiting center in the brainstem as well as the stimulation of the vagus nerve and the gastrointestinal tract [8]. This results in the suppression of nausea and vomiting induced by various stimuli, such as chemotherapy, radiation therapy, surgery, or motion sickness.

Granisetron has a high specificity for the 5-HT3 receptor and does not interact with other serotonin receptors (such as 5-HT1, 5-HT2, or 5-HT4), dopamine receptors, muscarinic receptors, histamine receptors, or opioid receptors. This explains why granisetron has few side effects and does not affect other physiological functions, such as mood, cognition, motor activity, or gastrointestinal motility.

Clinical efficacy

Numerous clinical trials have shown that granisetron is effective in preventing and managing CINV. Granisetron has been shown to be highly effective as a single agent or in combination with other antiemetics in a variety of chemotherapy regimens and emetogenicity levels. The efficacy of the drug extends to both the acute and delayed phases of CINV, providing patients with significant relief during their cancer treatment.

Safety profile

Granisetron has a favorable safety profile and is generally well tolerated. Granisetron, unlike some other antiemetic agents, does not cause significant sedation, allowing patients to maintain a higher quality of life during treatment. However, caution is advised for patients with known allergies or hypersensitivity to the drug [9].

Uses of granisetron

Granisetron is primarily used to prevent or treat nausea and vomiting caused by cancer therapy. Chemotherapy and radiation therapy can harm the cells that line the gastrointestinal tract, causing serotonin release from enterochromaffin cells [10-12]. Serotonin then binds to 5-HT3 receptors on vagal afferent nerves, which send signals to the brainstem vomiting center. Granisetron inhibits the transmission of nausea and vomiting signals by blocking these receptors.

Granisetron can be administered orally as a tablet or intravenously as an injection [13]. It is usually taken or administered prior to the start of chemotherapy or radiation therapy, and depending on the dose and regimen, it may be repeated after a certain interval. Granisetron has a high bioavailability (approximately 60%) and a long elimination half-life (approximately 9 hours), making it suitable for once-daily administration.

Granisetron is also available as a transdermal patch (Sancuso), which administers the drug continuously through the skin for up to 7 days. The patch is applied to the upper arm at least 24 hours before chemotherapy begins and removed at least 24 hours after chemotherapy concludes. The patch is a non-invasive and convenient alternative to oral or intravenous administration, particularly for patients who have difficulty swallowing or have poor venous access. The patch has the same efficacy and safety profile as granisetron taken orally [14, 15].

Granisetron may also be used to prevent or treat postoperative nausea and vomiting (PONV), which is a common complication of anesthesia and surgery [16]. PONV can affect up to 80% of patients undergoing certain types of surgery, such as abdominal, gynecological, or ear-nose-throat surgery. PONV can cause discomfort, dehydration, electrolyte imbalance, wound dehiscence, and delayed recovery. Granisetron can be given orally or intravenously before or after surgery to reduce the incidence and severity of PONV. Granisetron has been shown to be effective and well-tolerated in various clinical trials compared with other antiemetics, such as ondansetron, droperidol, or metoclopramide.

Granisetron may also help with gastroparesis, a condition characterized by delayed gastric emptying and symptoms such as nausea, vomiting, bloating, early satiety, and abdominal pain [17]. Diabetes mellitus, idiopathic factors, or medications that affect gastric motility can all cause gastropareses. Granisetron may improve gastric emptying by inhibiting serotonin-induced contraction and blocking 5-HT3 receptors on gastric smooth muscle [18]. A pilot study in patients with diabetic gastroparesis using the granisetron patch (Sancuso) showed promising results in terms of reducing nausea and vomiting frequency and improving quality of life. More research is needed, however, to confirm granisetron's efficacy and safety in this indication [19].

Dosage

The dosage of Granisetron varies depending on the route of administration and the condition being treated. The optimum dose of granisetron is 1 mg IV for PONV.

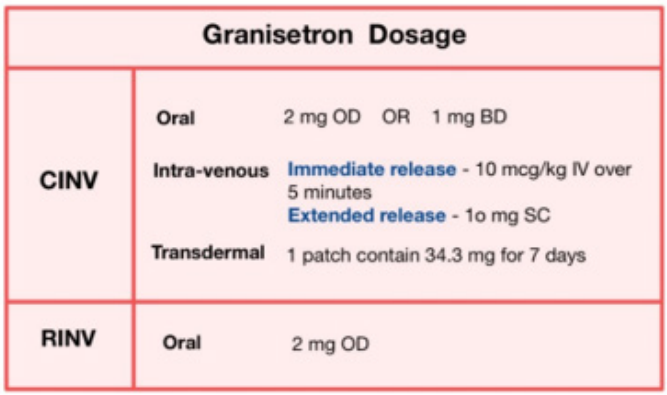

Figure 1: Granisetron dosage in Chemotherapy-Induced Nausea and Vomiting (CINV) [19] and Radiation-Induced Nausea and Vomiting (RINV) [21].

It is important to note that the dosage may need to be adjusted for patients with renal or liver impairment. It is always recommended to consult with a healthcare provider for specific dosage instructions.

Side effects of Granisetron

Granisetron has few side effects and is generally well tolerated. Headache, constipation, diarrhea, dizziness, fatigue, and injection site reactions are the most commonly reported side effects [20]. These side effects are typically mild and transient and do not require dose adjustment or discontinuation of therapy.

Unlike some other 5-HT3 receptor antagonists that can cause QT prolongation or hypotension, granisetron has no effect on cardiac conduction or hemodynamics [21, 22]. Granisetron, on the other hand, should be used with caution in patients with pre-existing cardiac conditions, electrolyte imbalances, or medications that can impair cardiac function. Granisetron should also be used with caution in patients with hepatic impairment, as it is metabolized by the liver and its clearance may be reduced in this population. Granisetron should be avoided in patients with hypersensitivity to granisetron or any of its components.

Granisetron is classified as pregnancy category B in the United States and category A in Australia [23], which means that there is no evidence of teratogenicity or fetal harm in animal studies [24], but there are no adequate and well-controlled human studies. Granisetron should only be used during pregnancy if absolutely necessary and after carefully weighing the potential benefits and risks. Granisetron is excreted in breast milk in trace amounts that are unlikely to harm a nursing infant. Breastfeeding mothers, on the other hand, should consult their doctor before using granisetron.

Latest research on granisetron

Granisetron is a well-known and widely used antiemetic with demonstrated efficacy and safety in a variety of clinical settings [20]. However, in terms of delivery methods, dosing regimens, combination therapies, and new indications, there is still room for advancement and innovation.

One of the most recent advancements in granisetron delivery is the development of a subcutaneous injection (Sustol) that employs a polymer-based drug delivery system that allows for 5-day granisetron release [25]. This formulation offers a convenient and effective option for patients requiring long-term antiemetic prophylaxis for chemotherapy-induced nausea and vomiting (CINV), particularly those receiving highly emetogenic chemotherapy regimens. Sustol was approved by the US Food and Drug Administration in 2016 for the prevention of acute and delayed CINV in adults.

Another novel granisetron delivery method is intranasal spray (Granisetrin), which provides a quick and non-invasive administration route that avoids first-pass metabolism and gastrointestinal absorption issues [26]. This formulation may be beneficial for patients who have difficulty swallowing or who have nausea or vomiting that prevents them from taking oral medications. Granisetrin has been shown in phase II and III clinical trials to be effective and well-tolerated in preventing CINV in adults.

A new indication for granisetron that is currently under investigation is the treatment of alcohol use disorder (AUD) [27]. Granisetron may have anti-craving and anti-relapse effects in AUD patients by modulating the mesolimbic dopamine system, which is involved in reward processing and addiction. Granisetron may also reduce alcohol-induced liver damage by inhibiting oxidative stress and inflammation mediated by serotonin. Several preclinical and clinical studies in animal models and human subjects with AUD have shown that granisetron reduces alcohol consumption, craving, withdrawal symptoms, and liver damage [28]. More research is needed, however, to confirm granisetron's efficacy and safety in this indication.

Conclusion

Granisetron has proven to be an invaluable asset in the management of CINV, significantly improving the quality of life for cancer patients undergoing chemotherapy. Granisetron has a favorable pharmacokinetic profile and can be administered orally, intravenously, transdermally, subcutaneously, or intranasally [29]. It is generally well-tolerated and has few side effects. Its potent antiemetic prop-

erties, combined with a favorable safety profile and a variety of administration options, have cemented its position as a cornerstone in antiemetic therapy. Granisetron's role in the supportive care of cancer patients is expected to remain pivotal as medical research advances, relieving the burden of CINV and allowing them to focus on their treatment and recovery. Granisetron may also be useful in treating gastroparesis or alcohol use disorder, but more research is needed to confirm these claims, as mentioned earlier.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

References

1. Tageja N, Groninger H (2016) Chemotherapy-induced nausea, and vomiting: an overview and comparison of three consensus guidelines. Postgrad Med J 92(1083): 34-40.
2. (1989) Granisetron: Prevents Emesis Despite Variable Pharmacokinetics. In Pharma 706(1): 5-5.
3. J P Terrey, M Aapro, V Kirchner, P Alberto (1995) 895 Patient Preference of Antiemetic Treatment: A Placebo Controlled, Double Blind Comparison of Granisetron with Granisetron Plus Dexamethasone. European Journal of Cancer vol. 31.
4. Chen R, Chen X, Wang H, Zhong W, Oh ES, et al. (2019) Pharmacokinetics, and safety of transdermal and oral granisetron in healthy Chinese subjects: An open-label, randomized, crossover study. Int J Clin Pharmacol Ther 57(1): 24-31.
5. Plosker GL, Goa KL (1991) Granisetron. A review of its pharmacological properties and therapeutic use as an antiemetic. Drugs 42(5): 805-824.
6. (2004) New Drugs: Granisetron. Australian Prescriber 27(4): 101-105.
7. Brooks P A, S R Glaum (1994) Brainstem 5HT3-receptor Mechanisms in the Central Nervous System. Pathophysiology 1(4): 269-270.
8. Johnston Kevin D, Zengbing Lu, John A Rudd (2014) Looking Beyond 5-HT3 Receptors: A Review of the Wider Role of Serotonin in the Pharmacology of Nausea and Vomiting. European Journal of Pharmacology 722: 13-25.
9. Giesele Kanny, E Beaudouin, D A Moneret Vautrin (2001) IgE-mediated allergy to granisetron and safe use of ondansetron. J Allergy Clin Immunol 108(6): 1059-1060.
10. Hsu YC, Chen CY, Tam KW, Chin Yu Hsu (2021) Effectiveness of palonosetron versus granisetron in preventing chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. Eur J Clin Pharmacol 77(11): 1597-1609. (2021).
11. Doggrell SA (2017) Granisetron in the treatment of chemotherapy-induced nausea and vomiting (CINV)- is there still a role after comparison with palonosetron? Expert Opin Pharmacother 18(10): 1019-1026.
12. Hamadani M, Chaudhary L, Awan FT, Khan JK, Kojouri K, et al. (2007) Management of platinum-based chemotherapy-induced acute nausea and vomiting: is there a superior serotonin receptor antagonist? J Oncol Pharm Pract 13(2): 69-75.
13. Soukop M (1994) Clinical experience with intravenous granisetron. Anticancer Drugs 5(3):281-286.
14. Haislip, Sally T (2013) Results from Four Pharmacokinetic Studies of the Granisetron Transdermal System. Research and Reports in Transdermal Drug Delivery, Informa UK Limited p. 19.
15. (2008) A granisetron patch (sancuso). Med Lett Drugs Ther 50(1301-1302): 103-104.
16. Stoops S, Kovac A (2020) New insights into the pathophysiology and risk factors for PONV. Best Pract Res Clin Anaesthesiol 34(4): 667-679.
17. Jung HK (2016) Symptomatic Improvement of Gastroparesis with Granisetron Transdermal System. J Neurogastroenterol Motil 22(4): 543-544.
18. McCallum RW, George SJ (2001) Gastric Dysmotility and Gastroparesis. Curr Treat Options Gastroenterol 4(2): 179-191.
19. Midani D, Parkman HP (2016) Granisetron Transdermal System for Treatment of Symptoms of Gastroparesis: A Prescription Registry Study. J Neurogastroenterol Motil 22(4): 650-655.
20. Spartinou A, Nyktari V, Papaioannou A (2017) Granisetron: a review of pharmacokinetics and clinical experience in chemotherapy induced - nausea and vomiting. Expert Opin Drug Metab Toxicol 13(12): 1289-1297.
21. Gavioli EM, Guardado N, Haniff F, Deiab N, Vider E (2021) The Risk of QTc Prolongation with Antiemetics in the Palliative Care Setting: A Narrative Review. J Pain Palliat Care Pharmacother 35(2): 125-135.
22. Mason JW, Moon TE, Oboyle E, Dietz A (2014) A randomized, placebo-controlled, four-period crossover, definitive QT study of the effects of APF530 exposure, high-dose intravenous granisetron, and moxifloxacin on QTc prolongation. Cancer Manag Res 6: 181-190.
23. Shapira M, Avrahami I, Mazaki-Tovi S, Shai D, Zemet R, et al. (2020) The safety of early pregnancy exposure to granisetron. Eur J Obstet Gynecol Reprod Biol 245: 35-38.
24. Caritis S, Zhao Y, Chen HJ, Venkataramanan R (2016) Pharmacodynamics of transdermal granisetron in women with nausea and vomiting of pregnancy. Am J Obstet Gynecol 215(1): 93(e1-4).
25. Barnes M, Calcanes G, Mosier MC, Vacirca J, Malik Z (2021) Granisetron Extended-Release Subcutaneous Injection versus Palonosetron Infusion for CINV Prevention: Cost Comparison of Unscheduled Hydration. Am Health Drug Benefits 14(3): 1-7.
26. Eissa EM, Elkomy MH, Eid HM, Ali AA, Abourehab MAS, et al. (2022) Intranasal Delivery of Granisetron to the Brain via Nanostructured Cubosomes-Based in Situ Gel for Improved Management of Chemotherapy-Induced Emesis. Pharmaceutics 14(7): 1374.
27. Kranzler HR, Soyka M (2018) Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA 320(8): 815-824.
28. Aboyoussef AM, Mohammad MK, Abo-Saif AA, Messiha BAS (2021) Granisetron attenuates liver injury and inflammation in a rat model of cecal ligation and puncture-induced sepsis. J Pharmacol Sci 147(4): 358-366.
29. Feyer P, Seegenschmiedt MH, Steingraeber M (2005) Granisetron in the control of radiotherapy-induced nausea and vomiting: a comparison with other antiemetic therapies. Support Care Cancer 13(9): 671-678.