

EMESIS DURING CHEMOTHERAPY: A REVIEW ON GRANISETRON, ITS EFFICACY AND DELIVERY SYSTEMS

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ABSTRACT

Nausea and vomiting are common problems occurs in disease, non-disease condition and after the chemotherapy, results from the activation of protective physiological mechanism in order to eliminate the toxin from the body. Principal four pathways that act on vomiting center to trigger nausea and vomiting are chemotherapy trigger zone (CTZ), cortex, peripheral pathway and the vestibular system. In emesis different treatment strategy are used in which Granisetron is a drug emerge as a drug of great potential to overcome chemotherapy induce nausea and vomiting. Current review aims to introduce emesis (CIE) during chemotherapy along with different novel therapeutic approaches and various clinical studies. In variety of studies to overcome the CIE novel approaches are of great importance.

Keywords: Emesis, Granisetron delivery system, Chemotherapy.

INTRODUCTION

Vomiting is medically known as "EMESIS". It is a forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. The feeling of about vomiting is called as nausea, which occurs as a precedes, but not always leads to vomiting [1]. Vomiting is a complicated process and includes a pre-ejection phase, ejection phase and post-ejection phase. In pre-ejection phase gastric smooth muscle relaxes and retrograde peristalsis. In ejection phase abdominal and diaphragmatic muscles contract [2]. In post-ejection phase come back to quiescent state [3].

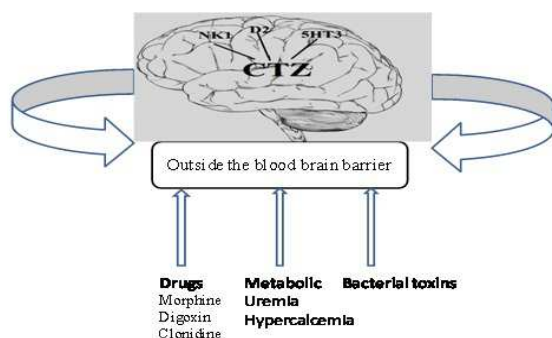


Fig. 1: Natural mechanism of controlling nausea and vomiting

There are 4 pathways that which originates the vomiting center to trigger nausea and vomiting i.e. chemotherapy trigger zone (CTZ), cortex, peripheral pathway and the vestibular system. The CTZ is exterior to blood brain barrier and reveal to toxins, i.e. chemotherapy and cerebral spinal fluid which triggers vomiting. In CTZ D₂, 5HT₃, NK1 neuro receptors are present. Dopamine receptor antagonists act in the neural pathway. Clozapine was the first typical antipsychotic. Antipsychotic are known to be used for nausea and vomiting. They act by obstruct the dopamine receptors which are class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system. The neurotransmitter dopamine is the main endogenous ligand for dopamine receptors [4].

Chemotherapy induced nausea and vomiting

Nausea and vomiting are the two most panic factors of chemotherapy. Various other causes of nausea and vomiting that are

linked with cancer or other treatments for example treatment with radiation block in the intestine caused by the tumor, reaction of medications, imbalance in body fluids [5].

Side-effects of chemotherapy [6]: 1. Fatigue 3. Nausea 5. Mouth sores
2. Hair loss 4. Vomiting 6. Bleeding

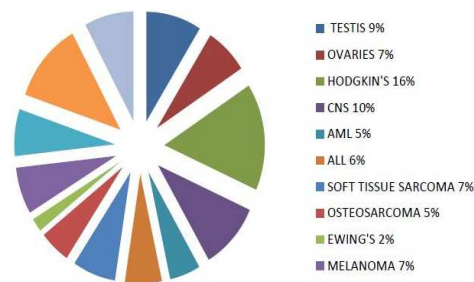


Fig. 2: Percentage prevalence of emesis in cancer patients undergoing chemotherapy

Classification of chemotherapy induced nausea and vomiting [7].

1. Acute CINV: It is the phenomena that occur in the first 24 h when patients received chemotherapy.
2. Delayed CINV: It is the phenomena that occur more than 24 h when patients received chemotherapy.
3. Anticipatory CINV: It is a learned response which occurs after patients CINV had poor controlled in the past.

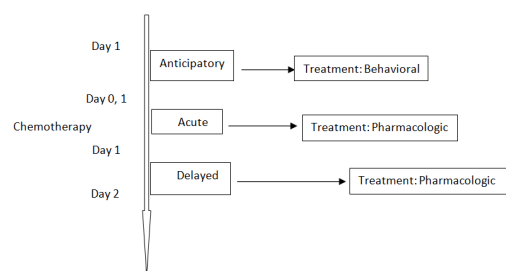


Fig. 3: Three types of chemotherapy induced nausea and vomiting: Timing and treatment

This diagram shows that line going along with the arrow on it told that Day1, Day 0, Day 1, Day 2, is usually chemotherapy. Chemotherapy is given on Day 0 in this anticipatory happen any time up until then. Acute is generally on the first day of treatment and then delayed is mentioned from Day 1 onward.

General risk factors and etiologies

Not all the cancer patients familiar the nausea and vomiting. [9] Several patient characteristics have also been identified. Includes the following points:

1. Occurrence and seriousness of nausea and vomiting during past courses of chemotherapy [10].
2. Background of chronic alcohol use [11].
3. Age: Nausea and vomiting more likely to be in younger patients than 50 y old [12].

4. Gender: Nausea and vomiting generally occurs in female [12].

Other possible causes are [13]

1. Fluid and electrolyte imbalances i.e. water intoxication and hypercalcemia.
2. Tumor invasion or growth in the GI tract, CNS.
3. Many drugs such as opioids.
4. Infection or septicemia.

Risk factors of chemotherapy induced and vomiting

Regimen that is joined to the high incidence ie.90% or higher of nausea or vomiting is referred as highly emetogenic chemotherapy and causing moderate incidence i.e. 30-90% is referred as moderately emetogenic chemotherapy [14].

Table 1: Grading methods for adverse events of nausea and vomiting: national cancer institute's [8]

Adverse event	Grade	Description
Nausea	1	Loss of appetite without alteration in eating habits
	2	Oral intake decreased without significant weight loss, dehydration or malnutrition.
	3	Inadequate oral caloric or fluid intake, tube feeding
	4	Grade not available
	5	Grade not available
Vomiting	1	1-2 episodes(separated by5 min) in 24 h
	2	3-5episodes(separated by5 min) in 24h
	3	>Episodes(separated by 5 min) in 24h; tube feeding, TPN
	4	Life threatening consequences; urgent intervention indicated
	5	Death

N& V= Nausea and vomiting (emesis); TPN= Total parenteral nutrition, ^aAdapted from National Cancer Institute (CTCEA version 4.0 2010), ^bDefinition: A disorder identify by a queasy sensation and/or the urge to vomit, ^cDefinition: A disorder identify by the reflexive act of ejecting the contents of the stomach through the mouth.

Table 2: Emetogenic risk-related with Interavenously (iv) administered Antineoplasticagents [15]

Level 1 Minimal risk,<10%	Vinblastin Bleomycin
Level 2 LOW RISK, 10-30%	Fluorouracil Topotecan
Level 3 Moderate risk, 31-90%	Doxorubicin Carboplatin
Level 4 HIGH RISK,>90%	Cisplatin Cyclophosphamide

The chemotherapy trigger zone (CTZ) is the region located in the area postrema and the nucleus solitaries (NTS) are the important relay areas for afferent impulses arising in the g. i. t throat and other viscera (KD Tripathi). The CTZ is having high level concentration of serotonin (5-HT₃), dopamine (D₂), and opioid receptors and the NTS is luxury in enkephaline, histamine and cholinergic receptors and 5-HT₃ receptors [16].

5-HT₃ Antagonists

It is a class of drug that work as receptor antagonists at 5-HT₃ receptor, a scientific serotonin receptor found in the terminals of vagus nerve and various areas of the brain [17].

History

The history begins in 1957, when two scientists J. H. Gaddum and Zuleika P. Picarelli offer the two serotonin receptor subtype M and D receptors i.e. morphine and dibenzylamine. In 1970's the scientists named Fozrad identified potent selective 5-HT₃ receptor antagonists ICS 205-930 from which first 5-HT₃ receptor antagonists ondansetron and granisetron were developed [18].

5-HT₃ Receptor

It is a member of the superfamily of the ligand-gated ion channels; it also includes the neuronal nicotinic acetylcholine receptors (nAChRs) and inhibitory neurotransmitter receptors for GABA and glycine.

It consists of 5 subunits arranged around a central ion conducting pore, which is permeable to sodium, potassium and calcium ions [19].

Receptors involved in various causes of nausea and vomiting [20].

Causes of nausea and vomiting Receptors involved

1. Cancer chemotherapy \rightleftharpoons Dopamine, Serotonin, Cannabinoid
2. Infection/inflammation \rightleftharpoons Cholinergic, Histamine, Neurokinin-1
3. Vestibular system dysfunction \rightleftharpoons Cholinergic, Histamine

Anti-Emetic

It is a drug that is powerful towards vomiting and nausea. There are generally used to treat motion sickness and the side effects of opioid analgesics, general anesthetics and chemotherapy administered against cancer [21].

Dopamine antagonists vanquish pro-emetic stimuli by blocking D2 receptors in the chemoreceptor trigger zone (CTZ).

5-HT₃ antagonists have been more recently progress to block the nausea and vomiting reflexes mediated by stimulation of 5-HT₃ receptors in both the small intestine and the CTZ.

Antihistamines, has widely being used in the migraine and generally used for motion sickness as they work at the level of the vestibular apparatus. Anticholinergic agents i.e. atropine and hyoscine are quite unsuccessful in the treatment of prevention of vomiting due to causes other than motion [22].

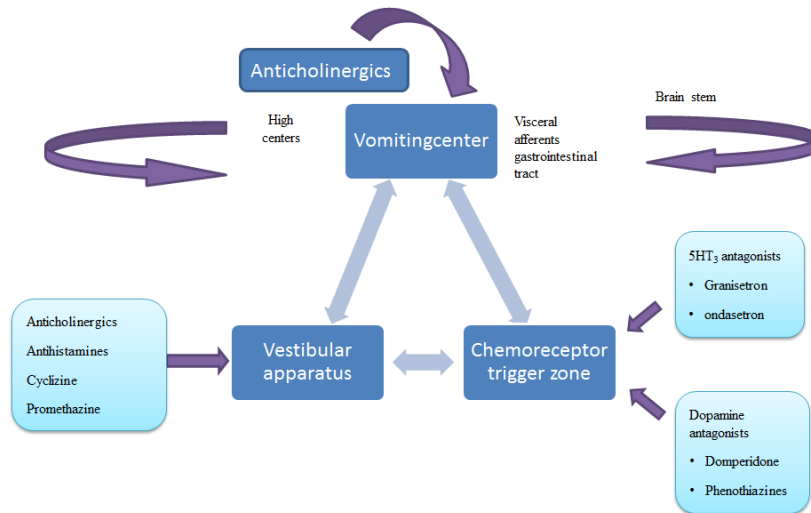


Fig. 4: Certain different sites of action of anti-emetics

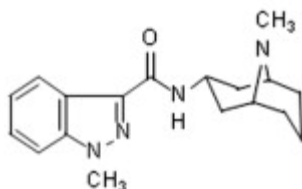
Table 3: Classification of 5-HT₃ receptor antagonists

Class	Dolasetron	Ondansetron	Granisetron	Palonosetron
Trade Name	Anzement ^R	Zofran ^R	Kytril ^R	Aloxi ^R
Half-Life	7.5	4	9	40
Receptor Binding Affinity Pki(nM)	7.7	8.1	8.4	10.4
Route of Administration	IV and Oral	IV and Oral	IV and Oral	IV Only

Drug: granisetron; Granisetron is a potent serotonin 5-HT₃ receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy. Common adverse events related with granisetron [23].

1	Constipation.
2	Diarrhea.
3	Asthenia.
4	Somnolence.
5	Headache.
6	Anemia
7	Infertility.

Structure of granisetron



Chemical formula: C₁₈H₂₄N₄O, Mol mass: 312.41 gm/mol

Pharmacokinetic profile

1. Bioavailability: 60%,
2. Protein binding: 65%,
3. Half-life: 3-14 h,

4. Log P: 2.64,
5. Log PK_a(9-14.7) not suitable for intestinal absorption,
6. Excretion: renal,
7. Dose: 1-2 mg

Mechanism of action of granisetron

It is a selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist with little or no affinity for other serotonin receptors including 5-HT₁, 5-HT_{1A}, 5-HT_{1B/C}, and 5-HT₂ or alpha 1 or alpha 2 or beta-adrenoreceptors for dopamine D₂, histamine H₁.

Serotonin receptors of the 5-HT₃ type are located peripherally on vagal nerve terminal and centrally in the CTZ of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells, release serotonin, which stimulates 5-HT₃ receptors.

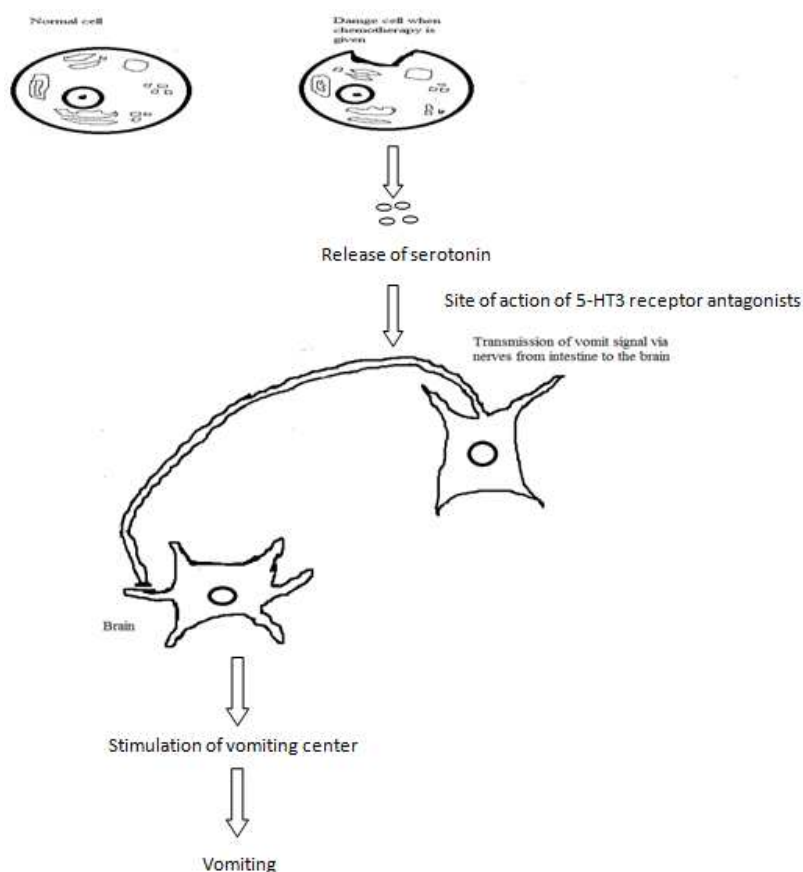


Fig. 5: Site of action of 5ht₃ receptor antagonists

Table 4: Formulation of granisetron approved by FDA

S. No.	Formulation	Invention	Year	Approved	Company
1.	Transdermal patch	SANCUSO (KYTRIL)	2008	FDA	Prostrakan
2.	Granisetron Hcl injection USP	KYTRIL ^R Injection	1993	FDA	PARENTA Pharmaceutical
3.	Granisetron tablets	Kytril tablets	1995	FDA	Roxane Laboratories
4.	Granisetron oral solution	Granisol ^R oral solution	2001	FDA	Aprius Pharmaceutical

Table 4: Advantage and disadvantage of various formulations

Formulation	Advantage	Disadvantage	Reference
1. Fast dissolving tablets.	1. Easy to administer. 2. Cost effective. 3. Pleasant mouth feel.	1. Hygroscopic in nature. 2. Requires special packaging.	[24]
2. Transdermal patch.	1. Provides a controlled release of medication. 2. Ease to apply.	1. Medications whose molecules are small enough to penetrate the skin can be delivered by this method.	[25]
3. Oral disintegration tablets.	1. Easy to administer geriatric, pediatric, mentally disabled, who cannot swallow the tablet. 2. The bioavailability is greater.	1. The ODT's size for both easy to swallow and easy to handle is difficult to achieve. 2. Expensive.	[26]
4. Injectables	1. Bypasses the digestive system. 2. More efficient usage.	1. Increased chance of infection. 2. Increased chance of infection.	[27]

Problems associated with the conventional dosage form

Conventional dosage form i.e. tablets or capsules are recent facing problems such as dysphagia, which follow high incidence of non-compliance and making the therapy inadequate [28] Problem associated with conventional oral dosage forms involve the mentally ill, the developmentally disabled, and patients who are uncooperative on taking less liquid-intake plans or are nauseated [29].

Challenges for development for novel formulation

1. The solubility landscape.
2. Low "hit" rate for novel drugs.
3. Increasing quality-Q &B.
4. Reducing the cost base.

5. Time to market.
6. Maximizing the product portfolio.
3. A nanoemulsion of granisetron.
4. Fast dissolving tablets of granisetron.

Various novel formulation of granisetron

1. Bilayer buccal tablets of granisetron.
2. Transdermal patches of granisetron.

In the field of formulating the granisetron dosage form a number of approaches including fast dissolving tablets, nanoemulsions, transdermal patch, bilayer buccal tablets etc have come in to play which is represented in table: 5,6,7,8.

Table 4: table showing problem regarding formulation and improvement in the formulation

Formulation	Problem regarding formulation	Improvement	Reference
1. Fast dissolving tablets.	1. Unpleasant taste [30]	Taste masking in FDTs is attained by adding sweet-tasting substances such as diluents, adding flavors or encapsulating the unpleasant drug in to micro particles or granules.	[31]
	2. Not enough mechanical strength.	Wow tab and durasolv Technologies can make tablets that are importantly hard and durable to allow them to be packed in multi-dose bottles.	[32]
2. Effervescent granules.	Instability in presence of moisture, problem in packing and storage. [33]	Stability of effervescent granules and powder is significantly enhanced by their packing in aluminum bags tightly closed.	[34]
3. Film coated tablets.	Film cracking [35]	PVA-PEG based polymer is successful in attaining the reduced process time and energy consumption, for the production of pharmaceutical formulations.	[36]
4. Injections	Pain [37]	Micro emulsion is a recent approach which has potential to reduce the pain on injection.	[38]

Table 5: Fast dissolving tablet of granisetron

S. No.	Ingredients used	Conclusion	Formulation type	Reference
1.	Sodium starch glycolate crosspovidone, mannitol, microcrystalline cellulose, sodium stearyl fumarate, granisetronHCl.	Drug release ($t_{50\%}$ 2.0 min)	Design of fast dissolving granisetronHCl tablets using novel co-processed superdisintegrants.	[39]
2.	GranisetronHCl, sodium bicarbonate, citric acid, tartaric acid, aspartame, flavor, talc, mannitol, sodium stearyl fumarate, croscarmellose sodium.	In-vitro dispersion time of 10 sec of formulation	Formulation design of fast dissolving tablet of granisetron using effervescent blend with improved efficacy.	[40]

Table 6: Nanoemulsion of granisetron

S. No.	Ingredients used	Conclusion	Formulation type	Reference
1.	Granisetron, lipoid E80, HPMC, HP- β -CD, tween80, sodium taurocholate, lauroglycol90, poloxamer188, penicillin, streptomycin.	Size of oil droplet was 50 nm.	A novel lipid nanoemulsion system for improved permeation of granisetron.	[41]
2.	GranisetronHCl, isopropylmyris-tate, n-methylpyrrolidone, tween85, ethanol, methanol.	No changes in long term stability and accerlating stability studies. 12 mo stable at room temperature.	Preparation and the in-vitro evaluation of nanoemulsion system for the transdermal delivery of granisetronHCl.	[42]

Table 7: Bilayer buccal tablet of granisetron

S. No.	Ingredients used	Conclusion	Formulation used	Reference
1.	Granisetron, sodium alginate, HPMC 50cps, carbopol 934p, polyvinylpyrrolidone K-30, polyethylene glycol4000,ethylcellulose, D-mannitol.	Final formulation having composition SA (47%W/W), CP (3%W/W), PVP (30%W/W) and DM (15%W/W) was found to be promising having in-vitro drug release of 94% in 8h along with bioadhesion strength (4.6g).	Formulation design and evaluation of bilayer buccal tablets of granisetronHCl.	[43]
2.	GranisetronHCl, sodium carboxymethylcellulose, HPMC15cps, carbopol 934p, ethyl cellulose, aspartame, magnesium stearate, D-mannitol.	Final formulation having composition HPMC cps (47% W/W), Carbopol 934p (3%W/W) and mannitol (45%W/W), was found to be promising having in-vitro release of 94% in 8h along with bioadhesion strength (4.3 gm).	Design and evaluation of buccoadhesive bilayer tablets of granisetronHCl.	[44]

Table 8: Transdermal patch of granisetron

S. No.	Ingredients used	Conclusion	Formulation used	Reference
1.	GranisetronHCl, Lutrol F-127, potassium dihydrogen phosphate, sodium hydroxide, silver chloride, silver wire.	It showed that the feasibility of granisetron transdermal patch transport through Lutrol F-127 gel by iontophoresis.	Enhanced transdermal delivery of granisetron by using iontophoresis.	[45]
2.	Crystalline granisetronHCl, amorphous granisetron patch, placebo patch, silicon low background sample holder.	Simpler and better technique for the crystallinity determination in transdermal patch.	An approach to determine crystalline content of granisetron in transdermal patches using X-ray diffraction technique.	[46]

Therapeutic use

The granisetron serves as an important therapeutic candidate in treating emesis during chemotherapy treatment. Now a day's

various combinations of granisetron with other drugs and granisetron alone are used in chemotherapy for the treatment of emesis. Table: 9 indicate the usage of granisetron in various clinical studies thus conforming its efficacy and safety status.

Table 9: Clinical studies (Comparative studies)

S. No.	Studies	Reference	Result	Conclusion
1.	Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double blind, phase III study.	[47]	In granisetron transdermal delivery system group headache is 0.3% which is lower as compared to oral granisetron group i.e. 2.5% but constipation was more frequent in GTDS i.e. 6.6% as compared to oral granisetron i.e. 3.1%.	The study indicates the GTDS (Granisetron transdermal delivery system) is well tolerated in cancer patients.
2.	Granisetron versus Dexamethasone in prophylaxis of nausea and vomiting after laparoscopic cholecystectomy.	[48]	In the first 24 h after operation, 7 patients in the dexamethasone group had nausea and 3 patients having vomiting. In granisetron group 5 patients had nausea and 2 have vomiting and there is no difference between the groups. In one case dexamethasone shows headache and in granisetron group one case show vertigo and one case headache. No difference in 2 groups in the regard (Pvalue: 0.614).	Concludes that dexamethasone and granisetron injection before anesthesia induction has same effects on nausea and vomiting prophylaxis after laparoscopic Cholecystectomy.
3.	Efficacy of generic granisetron vs. kytril for PONV in major gynecological operations: a randomized, double blind clinical trial.	[49]	In generic granisetron group there were 47 and 13 patients and in kytril group 45 and 15 patients experience hysterectomy and myomectomy. No dissimilarity between two treatment groups concerning postoperative nausea and vomiting control during 18 h after drugs administration.	Generic granisetron utilize efficacy against PONV after gynaeological surgeries which is non-inferior to that of kytril.
4.	Pre-treatment with intravenous granisetron to alleviate pain on propofol injection: a double blind, randomized, controlled trial.	[50]	24 patients (60%) objection on pain in the group pre-treated with normal saline as compared with six (15%) in the group pre-treated with granisetron. Pain was less in the granisetron group ($p < 0.05$). Seriousness of pain was also low in the granisetron group when related to the placebo group (2.5% vs.37.5%).	They conclude that pre-treatment with granisetron along with venous occlusion for 1 min for prevention of propofol-induced pain was highly successful.
5.	Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia.	[51]	About 36.7% patients had experience of nausea on day four of chemotherapy in ondansetron and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself($p = 0.001$). Extremely experience of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3 %($P = 0.003$). Though adverse effects like headache, constipation, abdominal pain and loose motions were reported in both group of children but there were less in children who receive granisetron. On the second day of therapy nausea and vomiting wax maximum in ondansetron and less in granisetron. On day 4 results was significant.	Conclude that to prevent acute and delayed chemotherapy induced and vomiting in children with all, oral granisetron is more effective as well as well tolerated with less adverse effect as compared to ondansetron.

CONCLUSION

Nausea and vomiting in cancer chemotherapy are highly distressing side effects in cancer treatment, development of effective combination chemotherapy regimens capable of prolonging lives and curing patients could not proceed until the parallel development

of highly effective, innovative CINV prevention and treatment strategies.

Among different treatment approaches the novel vesicular and particulate carrier are seems to be of great importance and have huge applications because of their targeting potential to act at

molecular basis and better control over tumor, restricted bio-distribution of drug as compare to conventional formulation. In various clinical studies 5-HT₃ antagonist more specifically granisetron and ondansetron was found to be of great importance in management of CINV but common adverse events include mild headache, transient elevation of hepatic aminotransferase levels, and constipation, however older 5-HT₃ antagonists (e. g., granisetron, ondansetron), have shown lower efficacy for the delayed type of chemotherapy-induced nausea and vomiting compared with the acute type, other category of drug neurokinin-1 (NK1) receptor antagonists aprepitant and fosaprepitant, and glucocorticoids were also seems to effective for CINV.

CONFLICT OF INTERESTS

Declared None

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