IJMPR 2021, 5(4), 30-38

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

A REVIEW ON PALONOSETRON - A POTENT 5-HT$_3$ RECEPTOR ANTAGONIST AND ITS THERAPEUTIC USES

Pungsh Tadar[1], Manikanta Murahari[2] and Mohammad Azamthulla[1]*

[1]Department of Pharmacology and [2]Department of Pharmaceutical Chemistry
Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru-560054, India.

Received on: 13/06/2021
Revised on: 03/07/2021
Accepted on: 23/07/2021

***Corresponding Author**
Mohammad Azamthulla
Department of Pharmacology, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru-560054, India.

ABSTRACT

5-HT$_3$ receptor antagonist have major role play in the management of neuro psychiatric and GIT disorders. Palonosetron is a newly generated 2nd generation of 5HT$_3$ receptor antagonist. FDA first approved Palonosetron in 2003 for prevention of acute nausea and vomiting associated with chemotherapy and used as antiemetic agent. It also used in pediatric patients to control sickness. The first generation of 5-HT$_3$ receptor antagonist such as ondansetron, granisetron, dolasetron and tropisetron are found to have similar efficacies in preventing acute cancer induced nausea and vomiting. Palonosetron hydrochloride is white to grayish, non-hygroscopic, glasslike powder, uninhibitedly dissolvable in water and dissolvable in methanol. It has two chiral focuses while the dynamic substance in the item comprises of a solitary stereoisomer. Palonosetron hydrochloride is known to show polymorphism. Its chemical name is (3aS)- 2-[(3S)- 1-azabicyclo[2.2.2]oct-3-l]- 2,3,3a,4,5,6-hexahydro-1H-benz[de]-isoquinolin-1-one hydrochloride relating to the atomic equation $C_{19}H_{24}N_{2O}$·HCl and has an overall sub-atomic mass of 332.87g/mol. The pharmacokinetics of Palonosetron have half-life around 40 hours and shows to be broadly appropriated in the body, bound to plasma proteins at an extent of 62%, processed by cytochrome P450 compounds, basically CYP_2D_6, with minor commitments from CYP_1A_2 and CYP_3A_4 and eliminates through urine. This review highlights the therapeutic, pharma kinetic and pharmacological properties of palonosetron that have been reported since 2003 and also displays the gaps in our knowledge about both the compounds and its characteristic limitations which deserves more exploration.

KEYWORDS: Palonosetron, 5-HT$_3$ Receptor, Antiemetic, Antagonist.

INTRODUCTION

FDA first approved Palonosetron in 2003 for prevention of acute nausea and vomiting associated with chemotherapy and concluded that it has greater activity than the rest of 5-HT$_3$ receptor antagonist.[1] Palonosetron is presently marketed in the USA for prevention of acute and delayed Cancer Induced Nausea and Vomiting (CINV). A statement was made in the study that a single dose of palonosetron can be helpful in the control of CINV and shows higher affinity and greater efficacy. Palonosetron have longer half-life compared to first-generation 5-HT$_3$ receptor antagonist subtype. Palonosetron has a similar tolerability outline to the first-generation 5-HT$_3$ receptor antagonists (RAs), exhibiting minimal side effects. Palonosetron have strong binding affinity for the receptor and little or no affinity for other receptors.[2] It is 2nd generation of serotonin antagonist called as setrons. The nausea and vomiting involving in Chemotherapy undergoing patients was observed to be the primary targets to control in order provide a good clinical chemotherapy treatment. The problem in the chemotherapy could delay or increase the duration of treatment and hospitalization. Emesis can developed due to activation of enterochromaffin cells present in the mucosa layer of GI and send signals to the chemoreceptor trigger zone (CTZ). The CTZ pooled the blood borne chemical signals with neuronal inputs and activating the vomiting center.[3] When the first generation 5-TH$_3$ was introduced in 1990, it had brought an advancement in the field of chemotherapy but still there were drawbacks to have complete control over the CINV. It is administered 30min before chemotherapy intravenously, as a single dose, or one hour before chemotherapy as a single oral capsule.

Palonosetron and its Characteristic Features[4]

Structure

Palonosetron hydrochloride is white to grayish, non-hygroscopic, glasslike powder, uninhibitedly dissolvable in water and dissolvable in methanol. It has two chiral focuses while the dynamic substance in the item comprises of a solitary stereoisomer. The total arrangement of the dynamic substance is (3aS, 3S). Palonosetron hydrochloride is known to show polymorphism. The assembling cycle, utilized by the

ASMF holder reliably yields Form I. Palonosetron micrograms is an infusion is a nonexclusive restorative item containing the dynamic substance Palonosetron. Palonosetron is a 5-HT_3 receptor opponent with a solid restricting liking for this receptor and almost no binding for different receptors. It is introduced as a white to grayish translucent powder. It is unreservedly dissolvable in water and solvent in methanol. Synthetically it is (3aS)- 2-[(3S)- 1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a, 4,5,6-hexahydro-1Hbenz[de]isoquinolin-1-one.hcl relating to the atomic equation $C_{19}H_{24}N_{2O}$·HCl and has an overall sub-atomic mass of 332.87 g/mol. (Figure: 1).

Stability

Stability of active substance stored in the intended commercial active substance package, low-density polyethylene bag, for 36 months under long term conditions at 25ºC / 60% RH and for to 6 months under accelerated conditions at 40ºC/75% RH according to the ICH guidelines were provided.

Mechanism of Palonosetron[4]

Palonosetron is an intense and specific 5-HT_3 receptor adversary. Palonosetron was appeared to tie to 5-HT_3 receptors in mind locales engaged with the regurgitating reflex, including the core tractus solitarius, and the chemoreceptor trigger zone in the territory postrema. Different locales engaged with the antiemetic impact of Palonosetron incorporate 5-HT_3 receptors on vagal afferents. The vagal afferents give contribution to the focal emesis community (medulla) in light of serotonin discharge from enter chromaffin cells, which might be invigorated by chemotherapeutic specialists.

Affinity and Potency

Palonosetron has a 30 overlap higher liking for the 5-HT_3 receptor contrasted with the other original 5-HT_3 RAs. Palonosetron has higher intensity at the 5-HT_3 receptor, being three-crease stronger than granisetron and up to multiple times more powerful than ondansetron in creature models.[5] The unmistakable pharmacokinetics and elements showed by Palonosetron contrasted with original 5-HT_3 RAs seem to convert into a particular clinical profile, giving expanded alleviation from CINV.[6]

Pharmacokinetics

The pharmacokinetics of Palonosetron have been examined both in sound volunteers[7] and disease patients accepting exceptionally emetogenic cisplatin,[6] with by and large comparative energy being appeared in the two examinations. Intravenously managed Palonosetron (0.3–90 μg/kg) indicated in general disposal half-life estimations of around 40 hours as aftereffect of low leeway esteems (1.11–3.90 mL/min/kg) and a huge volume of conveyance (3.85–12.6 L/kg). At the right now endorsed IV portion of 0.25 mg, Palonosetron shows to be broadly appropriated in the body, with a volume of dispersion of 8.3 L/kg, and to be bound to plasma proteins at an extent of 62 % Palonosetron is processed by cytochrome P450 compounds, basically CYP2D6, with minor commitments from CYP1A2 and CYP3A4. Palonosetron eliminates through urine.[8]

Oral bioavailability is 6-13% in rodents, canines, and monkeys. The medication entered the blood-cerebrum hindrance and was moved in the little and internal organ. End from tissues was for the most part corresponded with end from plasma. Palonosetron was cleared principally by hepatic digestion. Plasma contained 10-12 metabolites after oral or intravenous organization in individual creature species. Two of the fundamental metabolites in people were appeared to have powerless movement at the 5-HT_3 receptor and are not expected to create clinically applicable pharmacological action. Discharge of radioactivity following oral organization of Palonosetron in rodents was 51% in pee and 41% in excrement.[9]

Adverse reactions of Palonosetron

The 2nd generation palonosetron exhibit a comparable safety profile than the 1st generation in terms of frequency.[10] The most commonly reported treatment-related adverse reactions include Headache (9%) and constipation (5%), generally of minor concentration.

Thereapeutic activity in combination therapy

Hajdenberg and colleagues have shown a combination program of palonosetron 0.25 mg with dexamethasone 8 mg to be safe and well tolerated, with the common reported adverse events that were of mild–moderate severit.[11] Additionally, the due to safety profile of Palonosetron.[12]

Cardiovascular safety

A hypothetical cardiovascular danger has been noted for a few original 5-HT_3. Outstandingly ondolasetron and tropisetron because of expanded cardiovascular conduction times, especially mean prolongation of the QTc span. Organization of Palonosetron 0.25 mg brought about a 1-to 3-ms increment in QTc span during stage III investigations, which contrasted well with ondansetron and dolasetron (both 5-ms).[13,10]

Pharmacological activity

Palonosetron 0.50-mg oral dose has been ideal for the prevention of CINV in patients receiving moderately emetogenic chemotherapy due to a numerical benefits in efficiency without a side effect disadvantage.[14]

The general incidence of PONV was lesser in the Ramosetron group than the Palonosetron group. From the study it can conclude that Ramosetron was more potent than Palonosetron in reducing the incidence and severity of nausea induced by IV-PCAopioid after lumbar spinal surgery.[15]

Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.[16]

Safety, pharmacokinetics and efficacy of palonosetron in pediatric pateints was done and they concluded that palonosetron at 3mcg/kg and 10mcg/kg was effective and safe in the pediatric population.[17]

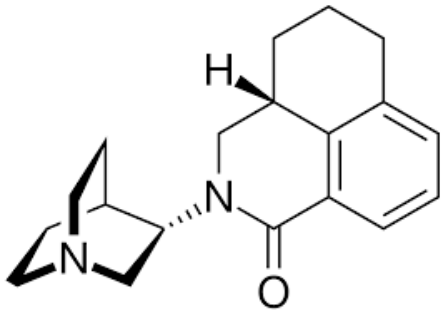

Figure 1: Chemical stricter of Palonosetron.

Toxicity profile[9]

Administration of 14 mg/kg/day was found to cause convulsion, reduced activity and death in rats during 6 months duration. Orally palonosetron was observed to be well tolerated and safe up to 60mg/kg/day in rats & mice and in dogs 20 mg/kg/day. At the dose 120mg/kg/day in 4 weeks major side effects was seen including anemia, hepatocellular swelling and glycogen deposition, decreased bone marrow cellularity, decreased femoral trabecular bone, multiple lesions in testes, immature spermatogenic cells in the epididymis, atrophy of lymphoid tissues, and chronic nephrosis. Oral administration of 180 mg/ kg/day in rats caused tremor, convulsion and mortality. Palonosetron is not mutagenic at dose of 10, 30, and 60 mg/kg/day in mice.

Tolerability[18]

When palonosetron was tested in human subjects in patients receiving chemotherapy.The intravenous and oral dosage forms of palonosetron were mostl reported to be well tolerated and safe. Infact the occurance of informed side effets was low (all <10%). Most of the observed addverse effeccts were considered to mild or moderate types and very few study were included to testify the withdrawals symptoms. The most common types of complaints were headache and constipation with the use of palonosetron.**[18]**

Pharmacoeconomic Concern[18]

When it comes to the Budget studies displayed on two European hospital perceptions in patients unloading MEC or HEC submitted pharmacoeconomic profits linked with the utilization of palonosetron compared with that of ondansetron or first-generation 5-HT3 receptor antagonists in the controlling of CINV. A huge US observational investigation stated a more encouraging financial gain with the use of palonosetron than with that of ondansetron for inhibiting CINV

Mixture of Palonosetron and Corticosteroid

The following studies have confirm that combinationtherapy with palonosetron with dexamethasone andaprepitant is well tolerrated and effectively prevents CINV associated with MEC and HEC.

Considering the Phase III registration studied by Aapro et al. of patients treating with HEC, two-thirds of members received dexamethasone 20 mg prophylactically. The dexamethasone-treated subgroup, the palonosetronarm displayed expressively higher CR rate than the ondansetron both in the delayed and overall phase.[10]

Saito et al. had conducted the first ever a double-blind randomised,comparative Phase III trial and prove the dominance of combination therapy with palonosetron 0.75 mg plus dexamethasone (n=555) compared with granisetron 40 µg/kg plus dexamethason.[19]

One more area of powerful examination is assessing the synergy effect of palonosetron plus examethasone with and without the addition of aprepitant. There have been three Phase II trials conducted, with 174 members in total. The use of combinational therapy with three-drug treatment containing palonosetron, dexamethasone and aprepitant conveyed similar CR in both acute and delayed phases. In each of these studies,the three-drug regimens were well tolerated and nounexpected severe side effects were reported. AAn nother area of intense investigation is evaluatingthe synergy between palonosetron anddexamethasone with and without the addition ofaprepitant (the only available NK-1RA and the focusof much recent clinical research). There have been three Phase II trials, with a total of 174 patientsenrolled: the use of a three-drug regimen comprising palonosetron, dexamethasone andaprepitant reported comparable CR in both acuteand delayed phases. In these studies,the three-drug regimens were found to be safe and effective.[20-21]

A Comparative Study of the Antiemetic Activity of Palonosetron and Granisetron in Breast Cancer Patients Treated with Anthracycline - Based Regimens[22]

When undergoing anthracycline‐based chemotherapy, with breast cancer patients nausea and vomiting is a huge disadvantage. A study was carried out to report, the results of palonosetron when compared with that of granisetron for patients who received anthracycline‐based chemotherapy.The efficacy of antiemetics of both the drugs were evaluated in the first cycle of chemotherapy, as well as the second and third cycles. For the study they selected a total of 21 patients and 19 patients and given palonosetrin and granisetron in the first cycle of chemotherapy, respectively. in the second chemotherapy cycle other antiemetic drug for (PALO followed by GRA or GRA followed by PALO) were switched to patients. A option were given to pateints to choose select between PALO or GRA antiemetics for the third cycle.21 patients choosed PALO and 18 patients selected GRA. in first and second cycles no substantial differences between PALO and GRA were recognised.

Though, during the third cycle, a important difference was detected in acute‑phase complete control of emetic events between the PALO and GRA treated groups, which was distinct as no emetic episode, no added antiemetic treatment and no more than mild nausea, between PALO and GRA. From these observation one can conclude that altering antiemetics drugs may affect the effectiveness of antiemetics. Thhe study have suggested that changing of antiemetic treatments, comprising drug combination and order of treatmentt, may expand the effect of antiemetic treatment.

The Effect of Palonosetron Hydrochloride in the Prevention of Chemotherapy-Induced Moderate and Severe Nausea and Vomiting[23]

The current study aimed to evaluate the efficacy and safety of palonosetron hydrochloride injection for preventing chemotherapy-induced moderate and severe nausea and vomiting. A multi-centered, randomly stratified, double-blind, double-dummy, parallel-group and positive-controlled trial was performed. A total of 240 patients who underwent chemotherapy treatment which induced moderate or severe vomiting were divided into the experimental and control groups. Half an hour before chemotherapy, the experimental group received a 0.25-mg palonosetron hydrochloride injection, whereas the control group received a 3-mg granisetron injection. The acute vomiting complete remission rate (CRR) of the experimental group was not significantly different compared with that of the control group (P=0.35). The delayed vomiting CRR of the experimental group was significantly higher compared with that of the control group (P=0.002). No difference in full course vomiting CRR, vomiting control time, treatment failure time or acute nausea CRR was identified between the two groups. No significant differences in adverse events were observed between the experimental group and the control group. No significant differences in adverse reactions occurred between the experimental group and the control group (12.50%). Palonosetron hydrochloride injection had a better effect on delayed vomiting CRR than granisetron hydrochloride injection. The two injections exhibited similar effects on acute vomiting CRR, full course vomiting CRR, vomiting control time, treatment failure time (days), acute nausea CRR and adverse events.

Palonosetron Exhibits Higher Total Control Rate Compared to First‑Generation Serotonin Antagonists and Improves Appetite in Delayed ‑ Phase Chemotherapy‑Induced Nausea and Vomiting[24]

In order to ensure the continuity of chemotherapy, it is crucial to provide appropriate supportive care to prevent chemotherapy‑induced nausea and vomiting (CINV). The frequency of CINV is greatly affected by the type and combination of chemotherapy employed, which requires further investigation. With the use of patient diaries, a prospective study on the efficacy of antiemetic regimens for nausea and vomiting was conducted in 103 patients receiving highly or moderately emetogenic chemotherapy in the Ambulatory Therapy Center of our institution between August, 2010 and March, 2011. In this study, the efficacy of palonosetron in the delayed phase was affirmed. on days 4 and 5, in particular, palonosetron exhibited a significantly higher efficacy compared to that of other conventional serotonin (5‑HT3) receptor antagonists (5‑HT_3RAs). When the effects of chemotherapy on food intake were assessed by switching granisetron to palonosetron, an improvement in appetite was observed in one‑quarter of the cases in the delayed phase. In addition, palonosetron has not been associated with any severe adverse drug reactions. It was therefore suggested that the use of palonosetron be recommended as a 5‑HT_3RA. In conclusion, the data suggested that palonosetron is effective and may be used as a 5‑HT_3RA, since it is crucial that we take adequate measures against CINV in order to maintain the patients' quality of life and to develop antiemetic regimens that ensure the continuity of chemotherapy without dose reduction.

Recent Development with the 5-HT_3 Receptor Antagonist for the Neuropsychaitric and GIT Disturbance[25]

Schizoprenia

Schizoprenia was first used by a German psychaitrist Eugen Bleular in 1911 as a term to explain the patients state of " Splitting of mind"[26] The symptoms can be seen at very early stage of life 18- 30 years[27] Schizoprenia can be describe into 3 main types- positive, negative and cognitive.[28]

The basic pathophysiology of the disorder can involve many factors like several genes and also environmental role in the manifest of disease[29] The genomic studies were able to find numerous genes that was accountable for the development of schizoprenia. In 2008, overall 500 genes was targeted for the caruse of disorder.[30]

When it comes to the environmental factors, viral infections, perinatal obstetric problems, hormonol issue, maternal stress, malnutrition and drug abuse.[31] In the animal model, elevated corticosteroid hormone may interfere with the CNS development process. The similar phenomenon can consider in the human and thereby it can conclude that events like near-death, war, or injury can have a role to play in the development of the disease.[32]

5-HT_3 RECEPTOR ANTAGONIST IN THE MANAGEMENT OF SCHIZOPRENIA

The $5ht_3$ receptor antagonist can be potential target in the disease, especially for the negative and positive scizoprenia.[33] The role can be explain as the 5-HT_3 receptor are present in the high concentration in the portion of the brain that are necessary for the cognitive roles, emotional performance and stimulus. Moreover, the $5ht_3$ also interrelate with striatal dopamine system making them a strong candidate in the list[34] The fact

that clozapine shows greater affinity for the 5-HT_3 receptors than for D_2 receptors[35] These drugs are used as add-on therapies to the existing standard antipsychotic drugs. The result of the combination treatment was concluded to be encouraging, the setrons in add-on treatment were found to improved the patients conditions in negative and cognitive symptoms but not in the positive schizoprenia. In addition, the setrons would reduce the extrapyramidal side effects of antipsychotic drugs.[36] The mechanism of action by which antipsychotic drugs side effects supressed the by the setron are unsolved till date but it is reported due to their ability to reduce the glutamate secretion in the striatum.[37] The another reason that can be understand through which $5ht_3$ may reduce psychotic symptoms is their capability to inhibit the inhibitory GABA interneurons in the prefrontal cortex.[38-39]

Depression

It can say that depression affects the 3% of the population globally. It is a mental illnes, a mood disorder that affects the individual mind and emotional system. It is a feeling of sadness, emptiness, pessimitic thoughts, suicidal thoughts and insomnia.[40-41]

The etiology in development of depression involved both genetic and environmental factors[42] Generally it is believed that stress is the primary environmental factor that lead to depression but only half of the population experience such events in life. The genetic factors have a vital role to decide the individual sensitivity to stress.[43] In the environmental part factors like emotional, sexual and physical abuse, parental separation, divorce or drug abuse in the family can contribute in the development of depression.[44-45]

Role of 5-HT_3 receptor antagonist in depression

The antidepressant activity of 5-HT_3 receptor antagonist (ondansetron and zacopride) was first discovered in the 1990s. After few years it was learned that the antagonist would increase the effects of antidepressant drugs[46] while the agonism reduces their activity.[47] In order to understand the mechanism of 5-TH_3 in the mangement of depression many mechanism was proposed and it explained that the antidepressant activity involve regulation of various neurotransmitter system, fall in hypothalamus-pituitary-adrenal hyperactivity,elevated in oxidative stress and neuronal damage and correction of altetred neuroplasticity in the brain.[48]

Anxiety

Anxiety is basically define as the emotional reaction to aniticipated events, an internal turmoil experience by a person which can be charcterize by terror and suspicions.[31] The anxiety can be of doifferent types including a social phobia, separation anxiety disorder, panic disorder and generalized anxiety disorder etc.[49]

The etiology and pahophysiology that observed in the anxiety are some genes like FKBP5, FAAH and ADCYAP1. They have targeted to cause greater risk for anxiety disorder. These genes are responsible to incrase amygdala reactivity and decrease the amygdala connectivity to other parts of brain like hippocampus. The amydala in the brain have a pivitol role to operate in the development of anxiety. Since it act as body clock that responds to any threats near us and lead to produce the physiological responses of fear. In the studies like brain imaging, the amygdala was in hyper activation in the pateints suffering from anxiety disorder.[50-52]

Role of $5HT_3$ receptor antagonist in anxiety disorder

In the animal, it was observed that $5HT_3$ receptor antagonist like tropisetron and ondansetron exhibit anxiolytic effects in the amygdala and dorsal raphe nucleus.[53] Suprisely these antagonist shows more advantageous compared to the benzodiapenes in the management of anxiety because it has no withdrawal problems and do not induce sedative side effect[54]. In addition they have equal anxiolytic potential[55]

Drug abuse

Drug dependency can be majorly seen during adolescence period.[56] Substance like psychoactive or CNS depressant drugs can be misused and it can lead to addicton and abuse among consumers. Genetic and environment factors are again considered to the factors playing behind.[31]

Role of 5-HT_3 receptor antagonist in drug abuse

The 5-HT_3 receptor antagonist blocks the psychoactive substances induce activation of mesolimbic pathway by affecting the concenteration of dopamine in NAc, VTA, substantia nigra and dorsal raphe nucleus. Therfore it can bring down the cravings[57, 58] Various studies have suggested that 5-HT_3 inhibited the D_2 receptor prompt by coccaine, morphine and amphetamine.[59,60,61-64] Futhermore they also block the activation of $GABA_A$ receptors, indication to be potential treatment in the drug abuse. So basically, 5-HT_3 act by preventing the activation of mesolimbic pathway produce by the substances.[65]

Irritable bowel syndrome

It is a disorder of GIT, affecting 10% to 20% of the population between 30-40 years.[66] The symptoms involve instabilities in the bowel habits and abdominal pain. IBS(irritable bowel syndrome) patients also seem to exhibit pyschological disorder like depression or anxiety.[67]

Role of $5HT_3$ receptor antagonist in the IBS

Among the setron Granisetron was first drug to shown positive outcomes in the IBS disorder.[68] But most of studies were conducted with oldanseron and it had shown a rapid onsetof action and long duration.[69] The drug resulted in the improving the stools consistency, decreased the urgency and also help in the abdomina pain in the pateints suffering from the IBS disorder.[70] Cislansetron have shown reduction of IBS- symptoms.[71]

CONCLUSION

It has proven that oral palonosetron exhibit similar efficacy and safety margin when compared to 1st generation 5-HT RAs. Palonosetron a dose of 0.50 mg orally was found to be effective against CINV in patients receiving MEC as it had many advantages with minimal side effects. Palonosetron is superior than ondansetron or ramosetron in high risk patients undertaking laparoscopic operation as antiemetic agent and used to control sickness in children undergoing BMT and shown good efficacy and safety profile. Palonosetron also create a new option for combination therapy with very less to moderate side effects. The combination therapy involving palonosetron-dexamethasone are superior when compared with another combination involving ondansetron-dexamethasone. Thus it was concluded that palonosetron to be a brilliant accumulation in the treatment of chemotherapy inducing nausea and vomiting. Therefore, this review suggests more studies on the compound to explore its new findings.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Dean Dr. Bharath S, Dr. Anbu and Prof: CHS Venkataramana, Faculty of Pharmacy, Ramaiah University of Applied Science, Bangalore, and Karnataka, India.Department of Pharmacology, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences Bangalore, India.

CONFLICT OF INTEREST

The is no conflit of intrest among authors.

REFERRENCE

1. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, Macciocchi A, Grunberg S. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT_3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. Cancer, 2003; 98(11): 2473-82.
2. Grunberg SM, Koeller JM. Palonosetron: A unique 5-HT_3 receptor antagonist for the prevention of chemotherapy-induced emesis. Expert opinion on pharmacotherapy, 2003; 4(12): 2297-303.
3. Hornby PJ. Central neurocircuitry associated with emesis. The American journal of medicine, 2001; 111(8): 106-12.
4. Palonosetron Accord. Assessment report.1 April 2015 EMA/287566/2016 Committee for Medicinal Products for Human Use (CHMP)
5. Eglen RM, Lee CH, Smith WL, Johnson LG, Clark R, Whiting RL, Hegde SS. Pharmacological characterization of RS 25259-197, A novel and selective 5-HT_3 receptor antagonist, *In-vivo*. Br. J. Pharmacol, 1995; 114(4): 860-66.
6. Eisenberg P, MacKintosh FR, Ritch P, Cornett PA, Macciocchi A. Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study. Ann. Oncol, 2004; 15(2): 330-7.
7. Stoltz R, Cyong JC, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in US and Japanese healthy subjects. J. Clin. Pharmacol, 2004; 44(5): 520-31.
8. Wong EH, Clark R, Leung E, Loury D, Bonhaus DW, Jakeman L, Parnes H, Whiting RL, Eglen RM. The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. Br. J. Pharmacol, 1995; 114(4): 851-9.
9. David B. Joseph, Ph.D. Pharmacology/ Toxicology review and evaluation. Center for drug evaluation and research. Application number, 2008; 22-233: 25: 1-2.
10. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, Bertoli LF, Yunus F, Morrica B, Lordick F, Macciocchi A. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann. Oncol, 2006; 17(9): 1441-9.
11. Hajdenberg J, Grote T, Yee L, Arevalo-Araujo R, Latimer LA. Infusion of palonosetron plus dexamethasone for the prevention of chemotherapy-induced nausea and vomiting. Support. Care Cancer, 2006; 4(9): 467-71.
12. Grote T, Hajdenberg J, Cartmell A, Ferguson S, Ginkel A, Charu V. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. Support. Care Cancer, 2006; 4(8): 403.
13. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, Tonini G, Labianca R, Macciocchi A, Aapro M. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann. Oncol, 2003; 14(10): 1570.
14. Boccia R, Grunberg S, Franco-Gonzales E, Rubenstein E, Voisin D. Efficacy of oral palonosetron compared to intravenous palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: a phase 3 trial.
15. Roh GU, Yang SY, Shim JK, Kwak YL. Efficacy of palonosetron versus Ramosetron on preventing opioid-based analgesia-related nausea and vomiting after lumbar spinal surgery: a prospective, randomized and double-blind trial. Spine, 2014; 39(9): 543-49.

16. Laha B, Hazra A, Mallick S. Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: A Randomized controlled trial. Indian J. Pharmacol, 2013; 45(1): 24-30.
17. Kadota R, Shen V, Messinger Y. Safety, pharmacokinetics, and efficacy of palonosetron in pediatric patients: a multicenter, stratified, double-blind, phase 3, randomized study. J. Clin. Oncol, 2007; 25(18): 9570-78.
18. Sang LPH, Scott LJ, Palonosetron. Drugs, 2009; 69: 2257–2278.
19. Saito M, Aogi K, Sekine I et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol, 2009; 10: 115–124.
20. Grote T, Hajdenberg J, Cartmell a et al. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. J SupportOncol, 2006; 4: 403–408.
21. Grunberg SM, Dugan M, Muss H et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer, 2009; 17: 589–594.
22. Ohzawa, H., Miki, A., Hozumi, Y., Miyazaki, C., Sagara, Y., Tanaka, Y., Shiba, S., Joutoku, H., Sakuragi, M., Takehara, M. and Sakuma, Y., Comparison between the antiemetic effects of palonosetron and granisetron in breast cancer patients treated with anthracycline‐based regimens. Oncology letters, 2015; 9(1): 119-124.
23. Huang, J., Wang, X.J., Yu, D., Jin, Y.N., Zhen, L.Z., Xu, N., Liu, W., Deng, Y.C., Wu, S.X. and He, J., The effect of palonosetron hydrochloride in the prevention of chemotherapy-induced moderate and severe nausea and vomiting. Experimental and therapeutic medicine, 2013; 5(5): 1418-1426.
24. Ueda, H., Shimono, C., Nishimura, T., Shimamoto, M. and Yamaue, H., Palonosetron exhibits higher total control rate compared to first‐generation serotonin antagonists and improves appetite in delayed‐phase chemotherapy‐induced nausea and vomiting. Molecular and clinical oncology, 2014; 2(3): 375-379.
25. Juza R, Vlcek P, Mezeiova E, Musilek K, Soukup O, Korabecny J. Recent advances with 5-HT_3 modulators for neuropsychiatric and gastrointestinal disorders. Med. Res. Rev, 2020; 40(5): 1593-678.
26. Kuhn R, Cahn CH. Eugen Bleuler's concepts of psychopathology. Hist Psychiatry, 2004; 15(3): 361-366.
27. Häfner H, Maurer K, Löffler W, Riecher-Rössler A. The influence of age and sex on the onset and early course of schizophrenia. Br J Psychiatry, 1993; 162(1): 80-86.
28. Hill SK, Keshavan MS, Thase ME, Sweeney JA. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. Am J Psychiatry, 2004; 161(6): 996-1003.
29. Siever LJ, Davis KL. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. Am J Psychiatry, 2004; 161(3): 398-413.
30. Sun J, Kuo P-H, Riley BP, Kendler KS, Zhao Z. Candidate genes for schizophrenia: a survey of association studies and gene ranking. Am J Med Genet B Neuropsychiatr Genet, 2008; 147B(7): 1173-1181.
31. Ebenezer I. Neuropsychopharmacology and Therapeutics. Chichester, West Sussex; Hoboken, NJ: Wiley Blackwell, 2015.
32. Os JV, Selten J-P. Prenatal exposure to maternal stress and subsequent schizophrenia: the May 1940 invasion of the Netherlands. Br J Psychiatry, 1998; 172(4): 324-326.
33. Malaspina D, Corcoran C, Kleinhaus K, et al. Acute maternal stress in pregnancy and schizophrenia in offspring: acohort prospective study. BMC Psychiatry, 2008; 8(1): 71.
34. Ellenbroek B, Prinssen E. Can 5-HT3 antagonists contribute toward the treatment of schizophrenia? Behav Pharmacol, 2015; 26: 33-44.
35. Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. Mol Basel Switz, 2018; 23(8): 2087.
36. Wang RY, Ashby CR, Edwards E, Zhang JY. The role of 5-HT3-like receptors in the action of clozapine. J Clin Psychiatry, 1994; 55(suppl B23–26): 23-26.
37. Ohno Y, Shimizu S, Tokudome K, Kunisawa N, Sasa M. New insight into the therapeutic role of the serotonergic system in Parkinson's disease. Prog Neurobiol, 2015; 134: 104-121.
38. Chameau P, van Hooft J. Serotonin 5-HT3 receptors in the central nervous system. Cell Tissue Res., 2006; 326: 573-581.
39. Puig MV, Santana N, Celada P, Mengod G, Artigas F. In vivo excitation of GABA interneurons in the medial prefrontal cortex through 5-HT3 receptors. Cereb Cortex, 2004; 14(12): 1365-1375.
40. Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet, 2016; 388(10053): 1545-1602.
41. Villas Boas GR, Boerngen de Lacerda R, Paes MM, et al. Molecular aspects of depression: a review from neurobiology to treatment. Eur J Pharmacol, 2019; 851: 99-121.
42. Saveanu RV, Nemeroff CB. Etiology of depression: genetic and environmental factors. Psychiatr Clin North Am., 2012; 35(1): 51-71.

43. Gershon ES, Bunney WE, Leckman JF, Eerdewegh M, DeBauche BA. The inheritance of affective disorders: a review of data and of hypotheses. Behav Genet, 1976; 6(3): 227-261.
44. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. Eur Arch Psychiatry Clin Neurosci, 2006; 256(3): 174-186.
45. Schoedl AF, Costa MCP, Mari JJ, et al. The clinical correlates of reported childhood sexual abuse: an association between age at trauma onset and severity of depression and PTSD in adults. J Child Sex Abuse, 2010; 19(2): 156-170.
46. Smith WW, Sancilio LF, Owera-Atepo JB, Naylor RJ, Lambert L. Zacopride, a potent 5-HT3 antagonist. J Pharm Pharmacol, 1988; 40(4): 301-302.
47. Lefebvre H, Contesse V, Delarue C, et al. Effect of the serotonin-4 receptor agonist Zacopride on aldosterone secretion from the human adrenal cortex: in vivo and in vitro studies. J Clin Endocrinol Metab, 1993; 77(6): 1662-1666.
48. Nakagawa Y, Ishima T, Takashima T. The 5-HT3 receptor agonist attenuates the action of antidepressants in the forced swim test in rats. Brain Res., 1998; 786(1–2): 189-193.
49. Gupta D, Prabhakar V, Radhakrishnan M. 5HT3 receptors: target for new antidepressant drugs. Neurosci Biobehav Rev., 2016; 64: 311-325.
50. McClure EB, Monk CS, Nelson EE, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry, 2007; 64(1): 97-106.
51. Monk CS, Telzer EH, Mogg K, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces inchildren and adolescents with generalized anxiety disorder. Arch Gen Psychiatry, 2008; 65(5): 568-576.
52. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biol Psychiatry, 2006; 59(5): 424-429
53. Costall B, Kelly ME, Naylor RJ, Onaivi ES, Tyers MB. Neuroanatomical sites of action of 5-HT3 receptor agonist and antagonists for alteration of aversive behaviour in the mouse. Br J Pharmacol, 1989; 96(2): 325-332.
54. Faerber L, Drechsler S, Ladenburger S, Gschaidmeier H, Fischer W. The neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol, 2007; 560(1): 1-8.
55. Costall B, Naylor RJ. Anxiolytic potential of 5-HT3 receptor antagonists. Pharmacol Toxicol, 1992; 70(3): 157-162.
56. Johnston L, O'malley P, Bachman J, Schulenberg J. Monitoring the future. National survey results on drug use, 1975–2010. Second school students. Ann Arbor: Institute for Social Research, the University of Michigan, 2003.
57. Fakhfouri G, Rahimian R, Dyhrfjeld-Johnsen J, Zirak MR, Beaulieu J-M. 5-HT3 receptor antagonists in neurologic and neuropsychiatric disorders: the iceberg still lies beneath the surface. Pharmacol Rev., 2019; 71(3): 383-412.
58. Engleman EA, Rodd ZA, Bell RL, Murphy JM. The role of 5-HT3 receptors in drug abuse and as a target for pharmacotherapy. CNS Neurol Disord Drug Targets, 2008; 7(5): 454-467.
59. Pei Q, Zetterström T, Leslie RA, Grahame-Smith DG. 5-HT3 receptor antagonists inhibit morphine-induced stimulation of mesolimbic dopamine release and function in the rat. Eur J Pharmacol, 1993; 230(1): 63-68.
60. Imperato A, Angelucci L. 5-HT3 receptors control dopamine release in the nucleus accumbens of freely moving rats.Neurosci Lett., 1989; 101(2): 214-217.
61. McNeish CS, Svingos AL, Hitzemann R, Strecker RE. The 5-HT3 antagonist zacopride attenuates cocaine-induced increases in extracellular dopamine in rat nucleus accumbens. Pharmacol Biochem Behav., 1993; 45(4): 759-763.
62. Kankaanpää A, Lillsunde P, Ruotsalainen M, Ahtee L, Seppâlä T. 5-HT3 receptor antagonist MDL 72222 dose-dependently attenuates cocaine- and amphetamine-induced elevations of extracellular dopamine in the nucleus accumbens and the dorsal striatum. Pharmacol Toxicol, 1996; 78(5): 317-321.
63. Kankaanpää A, Meririnne E, Seppälä T. 5-HT3 receptor antagonist MDL 72222 attenuates cocaine- and mazindol-, but not methylphenidate-induced neurochemical and behavioral effects in the rat. Psychopharmacology, 2002; 159(4): 341-350.
64. De Deurwaerdère P, Moison D, Navailles S, Porras G, Spampinato U. Regionally and functionally distinct serotonin3receptors control in vivo dopamine outflow in the rat nucleus accumbens. J Neurochem. 2005; 94(1): 140-149.
65. Engleman EA, Rodd ZA, Bell RL, Murphy JM. The role of 5-HT3 receptors in drug abuse and as a target for pharmacotherapy. CNS Neurol Disord Drug Targets., 2008; 7(5): 454-467.
66. Niedziałek J, Pachla M, Kordyga A, Proć Ł, Soroka E, Olajossy M. Irritable bowel syndrome—psychiatric issues. Curr Probl Psychiatry, 2019; 20(1): 35-48.
67. Dekel R, Drossman DA, Sperber AD. The use of psychotropic drugs in irritable bowel syndrome. Expert Opin Investig Drugs, 2013; 22(3): 329-339.
68. Moore NA, Sargent BJ, Manning DD, Guzzo PR. Partial agonism of 5-HT3 receptors: a novel approach to the symptomatic treatment of IBS-D. ACS Chem Neurosci, 2013; 4(1): 43-47.
69. Kozlowski CM, Green A, Grundy D, Boissonade FM, Bountra C. The 5-HT3 receptor antagonist alosetron inhibits the colorectal distention induced depressor response and spinalc-fos expression in the anaesthetised rat. Gut., 2000; 46(4): 474-480.

70. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. Aliment Pharmacol Ther, 1999; 13(9): 1149-1159.
71. Andresen V, Montori VM, Keller J, West CP, Layer P, Camilleri M. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol, 2008; 6(5): 545-555.