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A REVIEW ARTICLE ON ONDANSETRON

***Miss Swati Gupta Mr. Devashish Jeena (Assistant Professor)**

India.

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***Corresponding Author: Miss Swati Gupta**

India.

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ABSTRACT

Ondansetron is a selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist widely used for the prevention and treatment of nausea and vomiting associated with chemotherapy, radiotherapy, and postoperative conditions. This review article aims to summarize the pharmacological properties, mechanism of action, clinical applications, efficacy, and safety profile of ondansetron.

Ondansetron works by blocking serotonin receptors both centrally in the chemoreceptor trigger zone and peripherally in the gastrointestinal tract, thereby inhibiting the vomiting reflex. It has shown significant efficacy in controlling acute chemotherapy-induced nausea and vomiting (CINV), with moderate effectiveness in delayed phases when combined with other antiemetic agents.

Clinical studies indicate that ondansetron is generally well tolerated, with common side effects including headache, constipation, and dizziness. However, concerns such as QT interval prolongation and potential cardiac risks have been reported, especially in high doses or susceptible populations.

In conclusion, ondansetron remains a cornerstone in antiemetic therapy due to its effectiveness and relatively favorable safety profile. Ongoing research continues to explore its expanded uses and improved combination therapies for enhanced patient outcomes.

INTRODUCTION

Nausea and vomiting are common and distressing symptoms frequently associated with chemotherapy, radiotherapy, postoperative conditions, and various gastrointestinal disorders. These symptoms not only reduce the quality of life of patients but may also lead to complications such as dehydration, electrolyte imbalance, and poor compliance with

therapeutic regimens. Over the years, significant advancements have been made in the management of these symptoms, with the development of effective antiemetic agents.

Ondansetron, a selective serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist, has emerged as a key drug in the prevention and treatment of nausea and vomiting. It was one of the first agents in its class to demonstrate high efficacy and safety, particularly in chemotherapy-induced nausea and vomiting (CINV). The drug acts by blocking serotonin receptors located both centrally in the chemoreceptor trigger zone and peripherally in the gastrointestinal tract, thereby inhibiting the emetic reflex.

Since its introduction, ondansetron has been widely used in clinical practice and has significantly improved patient care in oncology and surgical settings. Despite its effectiveness, ongoing research continues to evaluate its safety profile, optimal dosing strategies, and potential applications in other conditions such as pregnancy-related nausea and gastroenteritis.

This review article aims to provide a comprehensive overview of ondansetron, including its pharmacological properties, mechanism of action, clinical uses, efficacy, and safety considerations.

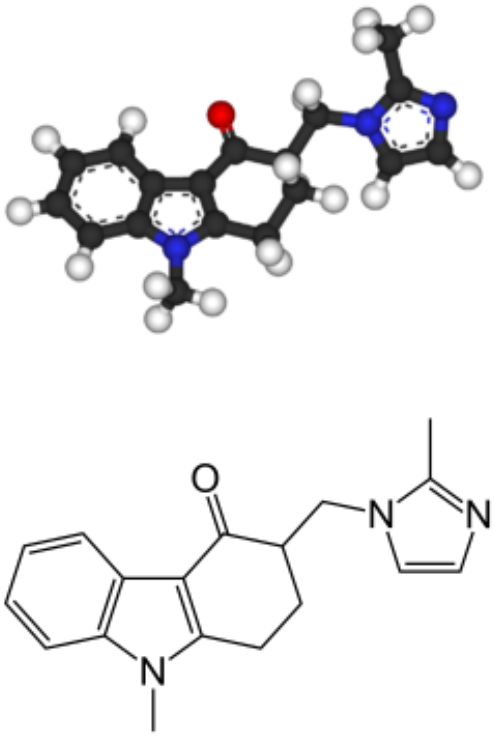
Chemical Structure

Chemical Structure Details:

- **IUPAC Name:**

9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4-one

- **Molecular Formula:** $C_{18}H_{19}N_3O$
- **Key Structural Features:**
  - **Carbazole ring system** (tricyclic aromatic structure)
  - **Imidazole ring** (nitrogen-containing heterocycle)
  - **Ketone group (C=O)** present
  - Lipophilic + basic nitrogen groups → receptor binding mein help karta hai



Mechanism of Action

Ondansetron is a highly selective serotonin (5-HT3) receptor antagonist widely used for its antiemetic effects. It belongs to a class of drugs that also includes other 5-HT3 receptor antagonists such as Granisetron, Dolasetron, and the newer agent Palonosetron.

The antiemetic action of ondansetron is mediated through both central and peripheral mechanisms. Centrally, it blocks 5-HT3 receptors in the chemoreceptor trigger zone (CTZ), which is located in the area postrema of the brain. This region plays a crucial role in detecting emetogenic stimuli such as circulating toxins and neurotransmitters, including serotonin, thereby initiating the vomiting reflex.

Peripherally, ondansetron inhibits 5-HT3 receptors present on the vagal nerve terminals in the gastrointestinal tract. These receptors are activated by serotonin released from enterochromaffin cells in response to irritants such as chemotherapy agents or gastrointestinal disturbances. The vagus nerve transmits these signals to the brainstem, particularly to the nucleus tractus solitarius, which coordinates the vomiting response.

Overall, the peripheral blockade of serotonin receptors is considered the primary mechanism responsible for the antiemetic efficacy of ondansetron, while central inhibition further enhances its therapeutic effect.

Pharmacokinetics

Absorption:

Ondansetron is rapidly absorbed following oral administration, reaching peak plasma levels within approximately 1.5 hours after an 8 mg dose. Its oral bioavailability ranges from 50% to 70%, mainly limited by first-pass hepatic metabolism. At higher doses (8–64 mg), bioavailability increases in a nonlinear manner due to partial saturation of this first-pass effect. Notably, patients with cancer exhibit higher bioavailability (around 85–87%) compared to healthy individuals, likely due to altered metabolic activity.

Distribution:

The drug is widely distributed throughout body tissues, with an apparent volume of distribution of about 1.8 L/kg at steady state. Ondansetron crosses the blood-brain barrier to a limited extent, with cerebrospinal fluid concentrations reaching only 10–15% of plasma levels. The presence of the ABCB1 transporter restricts its entry into the central nervous system by actively effluxing the drug. Reduced activity of this transporter may increase central drug concentration and enhance therapeutic efficacy.

Metabolism:

Ondansetron undergoes extensive hepatic metabolism, primarily through oxidation. The major metabolite formed is 8-hydroxy ondansetron, followed by smaller amounts of 7-hydroxy and 6-hydroxy metabolites. Minor metabolism also occurs via N-demethylation. Although 8-hydroxy ondansetron is pharmacologically active, it is rapidly conjugated and eliminated, contributing minimally to overall antiemetic action. The metabolism is mediated by cytochrome P450 enzymes, mainly CYP1A2, with additional contributions from CYP2D6 and CYP3A4, especially at higher drug concentrations.

Excretion:

Elimination of ondansetron occurs predominantly via hepatic metabolism, accounting for approximately 95% of its clearance, while less than 5% is excreted unchanged in urine. The elimination half-life in adults is typically 3–4 hours but may extend to around 5.5 hours in elderly individuals. Drug clearance varies with age, being higher in children and reduced in infants due to immature liver enzyme systems.

Administration

Ondansetron can be administered via multiple routes, including oral, intravenous (IV), and intramuscular (IM) methods. Oral preparations are available in conventional tablets as well as orally disintegrating tablets and soluble films, offering convenience in patients with difficulty swallowing.

For optimal effectiveness, the timing of administration is important. Oral ondansetron is typically given 1–2 hours prior to radiotherapy, about 30 minutes before chemotherapy, and approximately 1 hour before the induction of anesthesia. Both oral and intravenous formulations demonstrate comparable efficacy in managing chemotherapy-induced nausea and vomiting.

The dosage of ondansetron varies depending on the indication and route of administration. However, a single intravenous dose should not exceed 16 mg due to the increased risk of QT interval prolongation and potential cardiac arrhythmias. For the prevention of postoperative nausea and vomiting, standard dosing includes 8 mg orally every 12 hours or 4 mg administered intravenously.

Dose adjustment is generally not required in patients with renal impairment or those with mild to moderate hepatic dysfunction. However, in patients with severe hepatic impairment, the total daily dose should be limited to 8 mg, regardless of the route of administration. In pediatric patients, dosing is calculated based on body weight, typically 0.15 mg/kg per dose, with a maximum limit of 16 mg per dose.

Use in Specific Patient Populations

Hepatic Impairment:

Patients with mild to moderate hepatic dysfunction generally do not require dose modification. However, in cases of severe hepatic impairment, the clearance of ondansetron is significantly reduced, while its half-life and volume of distribution are increased. Therefore, caution is advised, and the total daily dose should not exceed 8 mg.

Renal Impairment:

Ondansetron does not require dose adjustment in patients with renal dysfunction, as its pharmacokinetics remain largely unaffected in such conditions.

Pregnancy:

Ondansetron was previously classified under FDA Pregnancy Category B and should be used cautiously during pregnancy. It is typically considered when first-line therapies fail to control

nausea and vomiting, including hyperemesis gravidarum. According to American College of Obstetricians and Gynecologists guidelines, initial treatment should involve pyridoxine alone or in combination with doxylamine. In resistant cases, ondansetron (e.g., 4 mg orally every 8 hours) may be used if clinically indicated. Some studies suggest a possible association between first-trimester exposure and congenital anomalies such as cleft palate, although evidence remains inconclusive. Monitoring of electrolytes and ECG is recommended in patients at risk of cardiac arrhythmias.

Breastfeeding:

Ondansetron is considered relatively safe during breastfeeding, as infant exposure through breast milk is minimal. It is commonly administered during and after cesarean section without affecting the initiation of breastfeeding. No significant adverse effects have been reported in breastfed infants. Additionally, ondansetron is approved for use in infants older than one month, and no special precautions are generally required.

Adverse Effects

Ondansetron is generally well tolerated; however, some adverse effects are relatively common. Frequently reported side effects (in more than 10% of adults) include headache, fatigue, dry mouth, malaise, and constipation. Less commonly, patients may experience central nervous system effects such as drowsiness or sedation, along with local reactions at the injection site and itching.

Mild and transient elevations in liver enzymes have also been observed, typically following a hepatocellular pattern. Although rare, clinically significant liver injury or jaundice has been reported in some cases.

Ondansetron may also cause changes in cardiac electrical activity, particularly QT interval prolongation on ECG. These effects are usually temporary, appearing within 1–2 hours after administration and resolving within 24 hours. Despite being uncommon, QT prolongation may predispose patients to serious arrhythmias such as torsades de pointes. The risk is higher with intravenous administration; therefore, a single IV dose should not exceed 16 mg. Rare cardiac events such as sinus bradycardia and asystole have also been documented.

Additional rare adverse effects include reduced gastrointestinal motility leading to intestinal obstruction and severe hypersensitivity reactions such as Stevens–Johnson syndrome, particularly in patients with multiple underlying conditions.

Drug–Drug Interactions

Caution is required when ondansetron is used concomitantly with other medications that affect cardiac conduction or serotonin levels. Co-administration with Pimozide should be avoided due to the increased risk of QT interval prolongation. Similarly, drugs like Amiodarone may further enhance this risk, necessitating careful monitoring.

Additionally, combining ondansetron with other serotonergic agents may increase the likelihood of developing serotonin syndrome, a potentially serious condition characterized by neuromuscular, autonomic, and cognitive disturbances.

Contraindications

Ondansetron should not be used in patients with known hypersensitivity to the drug or any of its components, as severe allergic reactions including anaphylaxis may occur. It is also contraindicated in individuals receiving Apomorphine, since their combined use can result in severe hypotension and possible loss of consciousness due to enhanced hypotensive effects.

Caution is advised in patients with phenylketonuria (PKU), particularly when using orally disintegrating formulations, as these may contain phenylalanine, which can lead to serious neurological complications in such individuals.

Monitoring

Monitoring is important in patients at risk of cardiac complications. Since ondansetron can cause dose-dependent QT interval prolongation, ECG monitoring along with assessment of serum electrolytes (potassium and magnesium) is recommended in high-risk populations. These include elderly patients, individuals with electrolyte imbalances (e.g., hypokalemia, hypomagnesemia), heart failure, bradyarrhythmias, or those taking other QT-prolonging drugs.

Routine monitoring is not necessary for all patients but should be considered in those receiving intravenous ondansetron or those with identifiable risk factors. In pregnant patients, monitoring should focus on potential fetal risks associated with drug exposure

Toxicity

There is no specific antidote available for ondansetron overdose, and management is primarily supportive. Reported cases of toxicity, particularly in infants, have included symptoms such as seizures, QT interval prolongation, liver toxicity, and features consistent with serotonin syndrome. Severe cases may require intensive supportive care, including airway management and the use of anticonvulsants like benzodiazepines.

Enhancing Healthcare Team Outcomes

Ondansetron is commonly used for the management of nausea and vomiting from multiple causes and is generally considered safe. However, careful monitoring is required in certain high-risk populations. Due to the possibility of dose-related QT interval prolongation, clinicians should monitor ECG and electrolyte levels (particularly potassium and magnesium) in vulnerable patients. These include elderly individuals and those with conditions such as hypokalemia, hypomagnesemia, heart failure, bradyarrhythmias, or concurrent use of other QT-prolonging medications. Routine pre-screening is not necessary in patients without identifiable risk factors.

Effective management of patients receiving ondansetron requires a coordinated interprofessional healthcare approach. Physicians are responsible for diagnosing and prescribing the medication appropriately, while specialists such as oncologists may be involved in cases of chemotherapy-induced nausea and vomiting. Pharmacists play a key role in verifying correct dosing, checking for drug interactions, and ensuring medication safety.

Nursing staff contribute by closely monitoring patients for therapeutic response and adverse effects, promptly reporting any concerns to the clinical team. In emergency situations, such as the occurrence of cardiac arrhythmias, emergency physicians must provide immediate stabilization. Severe or complicated cases may require involvement of intensivists for advanced care. In cases of overdose, consultation with a medical toxicologist may be necessary, and psychiatric evaluation is important if the overdose is intentional.

Overall, a collaborative team-based approach enhances treatment effectiveness, reduces medication errors, and improves patient safety. Evidence from clinical studies suggests that such interprofessional collaboration significantly minimizes adverse drug events and optimizes therapeutic outcomes.

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