Ondansetron

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Continuing Education Activity

Ondansetron is one of the medications most commonly used for the empiric treatment of nausea and vomiting. Ondansetron has excellent utility as an antiemetic drug, and it is effective against nausea and vomiting of various etiologies. Common uses of ondansetron include the prevention of chemotherapy-induced and radiation-induced nausea and vomiting, the prevention of postoperative nausea and vomiting, and off-label use for the prevention of nausea and vomiting associated with pregnancy. However, it is not effective for motion sickness-induced nausea. This activity will cover the mechanism of action, pharmacology, adverse event profiles, eligible patient populations, contraindications, and monitoring. It also highlights the interprofessional team's role in managing patients needing ondansetron therapy.

Objectives:

- Identify the antiemetic mechanism of action of ondansetron.
- Outline the approved and off-label indications for using ondansetron.
- Summarize the adverse event profile of ondansetron.
- Review the importance of improving care coordination among the interprofessional team to enhance the delivery of care for patients who can benefit from therapy with ondansetron.

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Indications

Nausea and vomiting are common complaints seen by emergency department physicians and primary care clinicians daily. Ondansetron is on the World Health Organization's (WHO) List of Essential Medicines, a list of medications considered effective and safe in meeting the essential needs of a health care system. Other antiemetics that appear on this list with ondansetron include dexamethasone and metoclopramide. In 2006 (the last year of its patent), the brand-name version of ondansetron was the 20th highest-selling brand-name drug in the United States, and its popularity continues today. Ondansetron has widespread utility as an antiemetic drug and is effective against nausea and vomiting of various etiologies.

The FDA-approved indications include the prevention of chemotherapy-induced nausea and vomiting(CINV), radiation-induced nausea and vomiting, and the prevention of postoperative nausea and vomiting (PONV). It is considered first-line therapy for the treatment of chemotherapy-

induced and radiation-induced nausea and vomiting.

Off-label use for the prevention of nausea and vomiting associated with pregnancy. Ondansetron has minimal efficacy against nausea and vomiting caused by motion sickness, mediated by different control centers and pathophysiologic mechanisms. There are limited data available from pediatric populations. Ondansetron is used in pediatric populations for the acute treatment of cyclic vomiting syndrome; however, there is little information available on the efficacy of this disease.Ondansetron is used off-label for severe refractory diarrhea associated with neuroendocrine tumors (carcinoid syndrome).

Mechanism of Action

Ondansetron is a selective 5-HT3 serotonin-receptor antagonist used for its antiemetic properties. It is one of the four FDA-approved 5-HT3 serotonin-receptor antagonists used to combat nausea and vomiting, including granisetron, dolasetron, and the second-generation drug, palonosetron.

Ondansetron acts both centrally and peripherally to prevent and treat nausea and vomiting. Central effects are mediated by the antagonism of 5HT-3 serotonin receptors in the area postrema. The area postrema, located on the fourth ventricle floor, contains the "chemoreceptor trigger zone." This zone senses neurotransmitters like serotonin, toxins, and other signals and plays a role in mediating the sensation of nausea and subsequent vomiting. Ondansetron also has effects peripherally by acting on the vagus nerve. It works on the 5-HT3 receptors that can be found at the vagus nerve terminals. The vagus nerve can sense nausea and vomiting triggers within the GI tract, such as stomach irritants. It forms synapses within the nucleus tractus solitarius of the brainstem, another region important in vomiting. The peripheral actions of ondansetron are thought to be the predominant mechanism for its antiemetic effects.

Pharmacokinetics

Absorption: Ondansetron undergoes rapid absorption from the GI tract, and the peak plasma concentration (Tmax) is approximately 1.5 hours after an 8 mg single oral dose. The absolute bioavailability of ondansetron after oral administration is approximately 60%(50%-70%). The lower bioavailability is attributed to first-pass metabolism. The systemic bioavailability of ondansetron increases nonlinearly with increasing doses from 8 mg, 16 mg, 32 mg, and 64 mg because of saturation of the first-pass metabolism. The bioavailability of ondansetron is significantly higher in patients with cancer (85% to 87%) than in healthy individuals (50%-70%), possibly due to alterations in metabolism.

Distribution: Ondansetron and its metabolites are extensively distributed in tissues. The apparent volume of distribution(Vd) at a steady state is approximately 1.8 L/kg. Ondansetron crosses the blood-brain barrier to a lower extent, with the CSF concentration only about 10%-15% of the plasma concentration in human volunteers. Adenosine binding cassette subfamily 1(ABCB1) is a

drug efflux transporter known to transport ondansetron across the blood-brain barrier, thus limiting its accumulation in the CNS. In a patient with decreased activity of ABCB1, the concentration of ondansetron in the brain increases and improves efficacy.

Metabolism: The liver is the primary site of metabolism. The primary mechanism of metabolism is oxidation. 8-hydroxy ondansetron represents the major metabolite (40%), followed by 7-hydroxy ondansetron (< 20%) and 6-hydroxy ondansetron (<5%). Minor metabolism also occurs via N-demethylation to yield N-demethyl ondansetron. The active metabolite of ondansetron is 8-hydroxy ondansetron which is rapidly metabolized to glucuronide and sulfate conjugates in the liver, resulting in low blood concentrations and, thus, a very small contribution to ondansetron's antiemetic activity. Cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4, are involved in the metabolism of ondansetron. In humans, CYP1A1/2 plays the most crucial role, while CYP2D6 plays a minor role in the metabolism of ondansetron. The role of CYP3A4 is important at higher concentrations of ondansetron.

Excretion: Hepatic metabolism accounts for nearly 95% of ondansetron clearance, and less than 5% is excreted unchanged in the urine. The clearance and elimination half-life of ondansetron vary according to age. The elimination half-life after an 8 mg oral or intravenous dose is approximately 3-4 h in adults, but on average, it is 5.5 hours in the elderly. Clearance ranges from 0.381 L/h/kg to 0.262 L/h/kg, depending on age. In adults, clearance is 0.351 5L/h/kg. The clearance per body weight is higher in younger children. However, the clearance is decreased in infants due to the underdeveloped cytochrome P450 enzyme system.

Administration

Routes of administration include oral, intramuscular (IM), and intravenous (IV). Oral formulations are available in dissolving tablet and soluble film forms. Ondansetron tablets should be administered 1 to 2 hours before radiotherapy, 30 minutes before chemotherapy, and an hour before anesthesia induction. Oral and IV formulations have been shown to have similar efficacy for treating emetogenic chemotherapy.

Dosing varies depending on the route of administration and the etiology. However, 16 mg per dose IV is the maximum recommended single dose due to the risk for QTc prolongation and arrhythmias. Standard dosing to prevent postoperative nausea and vomiting includes 8 mg every 12 hours orally or 4 mg given intravenously. No dosage adjustments are necessary for IV or oral administration in patients with renal impairment. The same holds for patients with mild to moderate hepatic impairment, but the maximum daily dosing is reduced to 8 mg IV or 8 mg orally in patients with severe hepatic impairment. Pediatric dosing is weight-based at 0.15 mg/kg per dose, with a maximum of 16 mg per dose.

Use in Specific Patient Populations

Patients with Hepatic Impairment: No dose adjustments of ondansetron are necessary for mild to moderate hepatic impairment. In patients with severe hepatic impairment, clearance of ondansetron is reduced; the volume of distribution and the plasma half-life is increased. Consequently, ondansetron should be used with caution, and the maximum recommended daily intravenous dose isis reduced to 8 mg.

Patients with Renal Impairment: No dosage adjustments are necessary for IV or oral administration in patients with renal impairment.

Pregnancy Considerations: Ondansetron is a former FDA "Pregnancy Category B" drug. It should only be used when other medications have been trialed and failed to treat pregnancy-associated nausea, vomiting, and hyperemesis gravidarum. According to ACOG(The American College of Obstetricians and Gynecologists) guidelines, pyridoxine alone or combined with doxylamine is the preferred pharmacological therapy for nausea and vomiting. However, in refractory cases with persistent symptoms, ondansetron, 4 mg orally every 8 hours, may be considered(if there is no dehydration). A possible association between ondansetron use in the first trimester and cleft palate has been reported. Electrolyte and electrocardiogram monitoring are suggested in patients treated with ondansetron having risk factors for arrhythmia, such as a family history of prolonged QT interval, heart failure, and electrolyte disturbances. Recommendations for pregnant women with gynecological cancer suggest that 5HT-3 antagonists (including ondansetron) can be used as supportive medication.

Breastfeeding Considerations: In a pharmacokinetic study, the relative infant exposure to ondansetron is less. Ondansetron is commonly used for nausea during and after a cesarean section, usually in doses of 4 to 8 mg intravenously. Using ondansetron during cesarean section does not affect the onset of breastfeeding. No adverse drug reactions have been reported in infants. Additionally, ondansetron is indicated for use in infants as young as one month. No specific precautions are required.

Adverse Effects

The most commonly reported side effects (occurring in more than 10% of adults) include headaches, fatigue, dry mouth, malaise, and constipation. Some less common effects range from central nervous system (CNS) manifestations, such as drowsiness and sedation, to local injection site reactions and pruritus. A transient increase in liver function tests has been reported as well. The pattern of liver enzyme elevation is normally hepatocellular, with rare cases of clinically apparent acute liver injury or jaundice.

Although typically clinically insignificant, EKG interval changes such as QTc elongation can be seen. These changes typically occur within 1 to 2 hours after administration, returning to baseline within 24 hours. As with any medication that causes QTc elongation, there is a concern for Torsade de Pointes and other arrhythmias. IV administration has a higher risk for arrhythmias; consequently, the FDA does not recommend a single dose greater than 16 mg IV. Isolated cases

of sinus bradycardia and asystole have also been reported. Cases of intestinal obstruction due to impaired gut motility have been reported. Stevens-Johnson syndrome has been reported in patients with multiple comorbidities.

Drug-Drug Interactions

Concurrent administration of pimozide with ondansetron should be avoided due to the risk of QTc prolongation. Amiodarone may also prolong the QTc interval; hence administration with ondansetron requires monitoring. There is a risk of serotonin syndrome when taking ondansetron in conjunction with other serotonergic medications.

Contraindications

Ondansetron is contraindicated in patients with hypersensitivity to the drug or any components of it. Severe hypersensitivity reactions, including anaphylaxis, have been reported. Ondansetron is also contraindicated in patients currently taking apomorphine. Concomitant use of ondansetron and apomorphine can lead to profound hypotension and loss of consciousness, with ondansetron enhancing the hypotensive effects of apomorphine. Patients with phenylketonuria (PKU) should be cautious, as the dissolving tablet formulation can contain phenylalanine, leading to irreversible neurological damage in PKU patients.

Monitoring

Due to the potential for dose-dependent QTc interval elongation, the FDA recommends EKG monitoring along with potassium and magnesium in susceptible populations, such as the elderly or other at-risk groups. These at-risk groups include patients with electrolyte abnormalities such as hypokalemia, hypomagnesemia, heart failure, bradyarrhythmias, or patients on other medications that may prolong the QTc interval.

Pregnant patients should be monitored for adverse fetal outcomes associated with ondansetron therapy. Current evidence does not suggest routine EKG and electrolyte monitoring for ondansetron without known risk factors. Monitoring should be done in high-risk patients receiving ondansetron intravenously.

Toxicity

There is no known antidote to ondansetron, and supportive measures are used for overdose. A case report describes an ondansetron overdose in an infant presenting with seizures, QTc prolongation, hepatotoxicity, and serotonin syndrome. The patient required endotracheal intubation, supportive care, and lorazepam for seizures.

Enhancing Healthcare Team Outcomes

Ondansetron is a widely prescribed medication for nausea and vomiting from various causes. The drug is relatively safe, but prescribers, including nurse practitioners, primary care providers, internists, surgeons, and emergency department physicians, need to monitor the drug in specific populations. Due to the potential for dose-dependent QTc interval prolongation, clinicians should monitor EKG, potassium, and magnesium levels in a susceptible population. It includes the elderly or patients with electrolyte abnormalities such as hypokalemia, hypomagnesemia, heart failure, bradyarrhythmias, or patients on other medications that may prolong the QTc interval. Current evidence does not demonstrate a need to pre-screen this population before administering ondansetron for patients without any of the above risk factors.

An interprofessional team approach is critical for diagnosing and managing symptoms, treating patients with nausea and vomiting, and managing the adverse effects of the treatments. Clinicians (MDs, DOs, NPs, PAs) usually prescribe ondansetron for labeled indications. Oncologist consultation is necessary for CINV. Pharmacists should ensure proper dose, perform medication reconciliation and consult prescribers about any concerns. Nursing staff should monitor patients administering medicine and inform clinicians of any side effects observed. Emergency department physicians should rapidly stabilize the patient in case of arrhythmia. Severe cases may require consultation with an intensivist and MICU/IMC level of care. Medical toxicologist consultation may become necessary in the overdose. If the overdose is intentional, psychiatric consultation is essential. An interprofessional team approach would maximize the efficacy and minimize potential adverse drug reactions for the patients requiring ondansetron, resulting in better patient outcomes. [Level 5] A prospective study involving 789 patients demonstrated that an interprofessional team approach among clinicians, residents, clinical pharmacists, and oncologists reduced potential medication errors, eventually enhancing patient safety. [Level 3]

Review Questions

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