Ondansetron Pharmacology and Indications: Review Article

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Abstract
The use of ondansetron, a selective serotonin 5-HT3 receptor antagonist, is well established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy or anaesthesia and surgery. The wide distribution of 5-HT3 receptors in the body and the role of these receptors in disease have provided the rationale for investigation of ondansetron in novel applications

KeyWords: Ondansetron, Serotonin Physiology.
DOINUMBER:10.48047/NQ.2022.20.19.NQ99383 **NEUROQUANTOLOGY2022;20(19):4195-4198**

Introduction:

Ondansetron, marketed under the brand name Zofran, is a medication used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery. It is also useful in gastroenteritis. It has little effect on vomiting caused by motion sickness**(1).**

Ondansetron was first used medically in 1990. It is on the World Health Organization (WHO) model list of essential medicines, the most important medications needed in a basic health system. It is available as a generic medication**(2)**.

Chemical structure:

Its chemical structure is (3RS)-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl] 1,2,3,9 - tetrahydro- 4H-carbazol - 4 - one hydrochloride dehydrate (Figure 1).

C18H19N3O

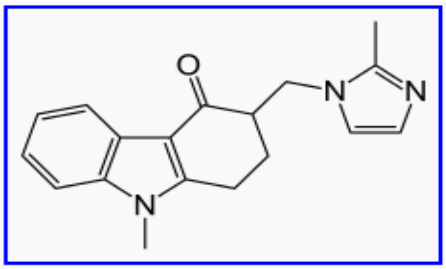

Figure (1): Chemical structure ofOndansetron(**3**)

Pharmacokinetics:

Ondansetron is completely and rapidly absorbed from the gastrointestinal tract after oral administration, and does not accumulate with repeated oral administration. Owing to hepatic first-pass metabolism, its bioavailability is only about 60% compared with ondansetron administered by infusion over 15 minutes. Possible alternative ways of administration of ondansetron include intramuscular, subcutaneous and rectal administration, and oral controlled-release formulations **(4).**

Ondansetron is widely distributed (volume of distribution approximately 160 L) and binds moderately (70 to 76%) to plasma proteins; the elimination half-life averages approximately 3.8 ± 1 hours. Clearance occurs by hepatic metabolism (95%) rather than renal excretion. Although aging is associated with decreased clearance and increased bioavailability, dosage adjustments are not required for the elderly, and may be necessary only in patients with severe hepatic impairment **(4).** It is broken down by the hepatic cytochrome P450 system and it has little effect on the metabolism of other drugs broken down by this system **(1)**.

Pharmacodynamic:

Ondansetron is a highly specific and selective5-HT3 receptor antagonist and with low

affinity for dopamine receptors. The 5-HT3 receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. Serotonin is released by the enterochromaffin cells of the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT3 receptors) to initiate the vomiting reflex. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites **(5).**

Ondansetron reduces the activity of the vagus nerve, which deactivates the vomiting center in the medulla oblongata, and also blocks serotonin receptors in the chemoreceptor trigger zone. It has little effect on vomiting caused by motion sickness, and does not have any effect on dopamine receptors or muscarinic receptors**(6)**.

Serotonin Physiology:

Serotonin, (5-HT), is present in large quantities in platelets and the gastrointestinal tract (GIT). It is also an important neurotransmitter in multiple areas of the central nervous system. Serotonin is formed by hydroxylation and decarboxylation of tryptophan. Monoamine oxidase inactivates serotonin into 5-hydroxyindoleacetic acid (5-HIAA). The physiology of serotonin is very complex because there are at least seven receptor types, most with multiple subtypes. The 5-HT 3 receptor mediates vomiting and is found in the GIT and the brain. The 5-HT 2A receptors are responsible for smooth muscle contraction and platelet aggregation, the 5-HT 4 receptors in the GIT mediate secretion and peristalsis, and the 5-HT 6 and 5-HT 7 receptors are located primarily in the limbic system where they appear to play a role in depression. All except the 5-HT 3 receptor are coupled to G proteins and affect either adenylyl cyclase or phospholipase C; effects of the 5-HT 3 receptor are mediated via anion channel **(5).**

Except in the heart and skeletal muscle, serotonin is a powerful vasoconstrictor of arterioles and veins. Its vasodilator effect in the heart is endothelium dependent. When the myocardial endothelium is damaged following injury, serotonin produces vasoconstriction. The pulmonary and renal vasculatures are very sensitive to the arterial vasoconstrictive effects of serotonin. Modest and transient increases in cardiac contractility and heart rate may occur immediately following serotonin release; reflex bradycardia often follows. Vasodilation in skeletal muscle can subsequently cause hypotension. Respiratory contraction of smooth muscle increases airway resistance and Bronchoconstriction. Hematological activation of 5-HT2 receptors causes platelet aggregation **(6).**

Indications of ondansetron:

Although an effective antiemetic agent, the high cost of brand-name ondansetron initially limited its use to controlling postoperative nausea and vomiting and chemotherapy-induced nausea and vomiting**(7)**.

1-Cancer treatment:

The 5-HT_3 receptor antagonists are the primary drugs used to treat and prevent chemotherapy-induced nausea and vomiting and radiotherapy-induced nausea and vomiting **(7)**.

2-Postoperative:

A number of medications including ondansetron appear to be effective in controlling postoperative nausea and vomiting. It is more effective than metoclopramide, and less sedating than cyclizine or droperidol**(7)**.

3-Pregnancy:

Ondansetron is used off-label to treat morning sickness and hyperemesis gravidarum of

pregnancy. It is typically used after trials of other drugs have failed **(8).**

4-Cyclic vomiting syndrome:

Ondansetron is one of several antiemetic agents used during the vomiting phase of cyclic vomiting syndrome**(9)**.

5-Post anaesthesia shivering:

Some studies showed its anti-shivering effect following both general and neuraxialanaesthesia**(10)**.

Ondansetron is better than pethidine because of its ability to reduce shivering from 50 to 13.3% in addition to less side effects especially in patients with hemodynamic instability **(11)**.

Contraindications and side effect :

Ondansetron is a well-tolerated drug with few side effects. diarrhea, dizziness, headache and confusion are the most commonly reported side effects associated with its use and other side effect include blurred vision or temporary vision loss (lasting from only a few minutes to several hours), high levels of serotonin in the body (agitation, hallucinations, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination and fainting), slow heart rate, trouble breathing, and increase in liver enzyme (transient) Serious side effects include QT prolongation and severe allergic reaction**(1)**.

Use of ondansetron has been associated with prolongation of the QT interval, which can lead to the potentially fatal heart rhythm known as torsades de pointes. Although this may happen in any patient with any formulation, the risk is most salient with the injectable intravenous form of the drug, and increases with dose. The risk is also higher in patients taking other medicines that prolong the QT interval, as well as in patients with congenital long QT syndrome, congestive heart failure , and/or bradyarrhythmias. As such, single doses of injectable ondansetron should not exceed 16mg at one time. Oral dosing recommendations remain intact, including the recommendation of a single 24-mg oral dose when indicated. Electrolyte imbalances should be corrected before the use of injectable ondansetron. Patients are cautioned to seek immediate medical care if symptoms such as irregular heart beat or palpitations, shortness of breath, dizziness, or fainting occur while taking ondansetron **(12)**.

Anecdotally, Ototoxicity has also been reported if ondansetron isinjected too quickly**(1)**.

Drug Interactions:

1) Apomorphine: It may lead to profound hypotension, loss of consciousness and sweating **(13).**
2) Tramadol: It may reduce its analgesic effect **(14).**

Overdose:

Overdose is rare and no fatal dose has been established. And no specific treatment is available for ondansetron overdose, patients are managed with supportive measures. An antidote to ondansetron is not known **(12)**.

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*e*ISSN1303-5150