Ondansetron hydrochloride injection

Classification:[1]

Antiemetic

Pharmacology[2]

Ondansetron is a selective 5-HT_3 receptor antagonist.

Indication[1,2]

Ondansetron injection is FDA approved for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, for prevention of postoperative nausea and/or vomiting, and for the prevention of further episodes of nausea and/or vomiting postoperatively in patients who did not receive prophylactic ondansetron but experience nausea and/or vomiting postoperatively.

Ondansetron injection is used off-label for the treatment of severe, acute undifferentiated nausea and/or vomiting, symptomatic treatment of nausea and vomiting in patients with gastroparesis, severe or refractory pregnancy-associated nausea and vomiting, and vertigo-associated nausea and vomiting.

Pharmacokinetics[2]

Pharmacokinetic Parameter	Details
Absorption	A study was completed to evaluate the pharmacokinetics of a single 4 mg dose of ondansetron administered as a 5-minute infusion compared with a single intramuscular injection. Systematic exposure measured by AUC was equivalent. Mean peak plasma concentrations at 10 minutes after IV infusion were 42.9 ng/mL (95% CI 33.9, 54.4) and at 41 minutes after intramuscular injection were 31.9 ng/mL (95% CI: 26.3, 38.6).

Pharmacokinetic Parameter	Details
Distribution	Plasma protein binding measured in vitro was 70-76% over the pharmacologic concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.
Metabolism	Extensively metabolized. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Nonconjugated metabolites with pharmacologic activity are not found in plasma at concentrations likely significant to contribute to pharmacologic activity of ondansetron.
Excretion	In adult cancer patients, the mean elimination half-life was 4 hours, with no difference in multidose pharmacokinetics over 4 days.

Dosage/Administration[1,2]

Prevention of postoperative nausea and vomiting, adults: 4 mg IV as a single dose at the end of surgery.

Severe acute nausea and vomiting, adults (off label use): 4 mg as a single dose IV or IM.

Use in Special Populations[2]

Pregnancy: Published epidemiological studies on the associated between ondansetron and fetal outcomes have reported inconsistent findings and have methodological limitations. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when administered IV during organogenesis at approximately 3.6 and 2.9 times the recommended human IV dose of 0.15 mg/kg given three times a day, based on body surface area, respectively. Risks and benefits should be considered in this population.

Lactation: It is unknown whether ondansetron is present in human milk and there are no data on the effects of ondansetron in a breastfed infant or the effects of milk production. It has been shown that ondansetron is present in the milk of rats. Risks and benefits should be considered in this population.

Pediatric Use: Clearance of ondansetron in pediatric patients aged 1 to 4 months is slower and the half-life is about 2.5-fold longer than patients who are aged 5 to 24 months. It is recommended that patients younger than 4 months be monitored closely.

Geriatric Use: No overall differences in safety or effectiveness were observed between subjects 65 years and older and younger subjects. A reduced clearance and increased in elimination half-life were seen in patients older than 75 years compared to younger subjects, but there were an insufficient number of patients older than 75 years in the clinical trials to draw conclusions about safety and efficacy in this group compared to younger subjects.

Hepatic Impairment: Clearance is reduced and apparent volume of distribution is increased (with a resulting increase in plasma half-life) in patients with severe hepatic impairment (Child-Pugh score of 10 or more). In these patients, the max total daily dose is 8 mg.

Renal Impairment: Plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 ml/min), but no dosage adjustment is recommended.

Contraindications[2]

Contraindicated with a known hypersensitivity to this product or its components. The concomitant use of apomorphine with ondansetron is contraindicated based on reports or profound hypotension and loss of consciousness with apomorphine is administered with ondansetron.

Precautions

- **Hypersensitivity:** Hypersensitivity reactions have been reported, including in patients who have had hypersensitivity to other selective 5-HT_3 receptor antagonists.
- **QT Prolongation:** Ondansetron can cause dose-dependent QT interval prolongation and postmarketing cases of Torsade de Pointes have been reported. Ondansetron should be avoided in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medications that prolong the QT interval.
- **Serotonin Syndrome:** Serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports were associated with use of concomitant serotonergic drugs. Reports of serotonin syndrome have also been reported with ondansetron overdose. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonists use occurred in a post-anesthesia care unit or an infusion center.
- **Masking Progressive Ileus and Gastric Distension:** Ondansetron use after abdominal surgery or in patients with chemotherapy-induced nausea or vomiting may mask a progressive ileus and gastric distension.

- **Effect on Peristalsis:** Ondansetron does not stimulate gastric or intestinal peristalsis and should not be used instead of nasogastric suction.

Adverse Effects[2]

In studies of postoperative nausea and vomiting, adverse reactions reported in greater than 2% (and with greater frequency than the placebo group) of adult patients receiving ondansetron included:

Adverse Reaction	Ondansetron Injection 4 mg IV over 2-5 min (n = 547)	Placebo (n = 547)
Headache	92 (17%)	77 (14%)
Drowsiness/sedation	44 (8%)	37 (7%)
Injection site reaction	21 (4%)	18 (3%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (<1%)
Paresthesia	9 (2%)	2 (<1%)

Adverse reactions in postmarketing experience has included arrhythmias, bradycardia, electrocardiographic alterations, palpitations, syncope, flushing, hypersensitivity reactions, liver enzyme abnormalities, local injection site reactions, hiccups, dystonic reactions, transient dizziness, urticaria, Stevens-Johns syndrome, topic epidermal necrolysis, and cases of transient blindness or transient blurred vision.

Monitoring[1]

Patients should receive an ECG if they are at risk for QT interval prolongation, and potassium and magnesium should be monitored. Monitor for signs of serotonin syndrome and for decreased bowel activity.

Interactions[1]

Ondansetron does not induce or inhibit the cytochrome P-450 system. Ondansetron is metabolized by hepatic enzymes CYP3A4, CYP2D6, and CYP1A2, and inducers or inhibitors of these enzymes may change the clearance and half-life of ondansetron. No dosage adjustments are recommended in patients on these drugs.

Apomorphine: Concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when these medications were administered together.

Phenytoin, Carbamazepine, and Rifampin: These potent inducers of CYP3A4 increase the clearance of ondansetron and decrease blood concentrations of ondansetron. No dosage adjustment for ondansetron is recommended based on available data.

Tramadol: Concomitant use of ondansetron with tramadol may result in reduced analgesic activity of tramadol, based on two small trials. Patients in these trials self-administered tramadol more frequently when on concomitant ondansetron.

Serotonergic drugs: Serotonin syndrome has been seen with concomitant use of 5-HT3 antagonists and other serotonergic drugs.

Efficacy[2,3]

The use of ondansetron for acute nausea and vomiting not associated with surgery or chemotherapy has mainly been evaluated in the emergency department (ED) setting. A Cochrane Systematic Review published in 2015 analyzed the evidence of antiemetic medications in the treatment of nausea and vomiting in adult ED patients. Eight trials were included with 952 participants. The primary outcome was mean change in visual analog scale (VAS) (1 to 100) for nausea severity from baseline to 30 minutes. In this review, ondansetron was not statistically significantly superior to placebo. When antiemetic medications were compared to active controls, one medication was not identified as being superior than others. Overall, the quality of evidence was low due to a lack of data.

Ondansetron was also evaluated in 441 adult patients who experienced postoperative nausea and/or vomiting but did not receive prophylactic antiemetic. Patients who experienced nausea and/or vomiting received ondansetron 4 mg IV over 2-5 minutes, and it was found to be significantly more effective than placebo, as measured by number of emetic episodes, time to first emetic episode, and mean nausea score over 24-hours after surgery.

Dosage Forms/Cost[4]

Name	Strength	Package size	AWP Unit Price
Ondansetron HCl (solution)	2 mg/1mL	2 mL	$0.16 - $1.25

Special Considerations

None

Summary/Conclusion

Ondansetron injection has been shown to be effective in postoperative nausea and/or vomiting, but the efficacy compared to placebo in high-quality trials of nausea and/or vomiting not associated with surgery or chemotherapy is lacking. Smaller trials for nausea and/or vomiting not associated with surgery or chemotherapy suggest that ondansetron may be beneficial.

Recommendation

It is recommended to add ondansetron injection to the current formulary. An alternative route of administration of this antiemetic may be beneficial in patients who cannot tolerate oral medications.

References

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