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REVIEW

Reappraisal of the role of dolasetron in prevention and treatment of nausea and vomiting associated with surgery or chemotherapy

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Abstract: Chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting are one of the most frequent but also very concerning consequences for patients undergoing chemotherapy or surgical procedures under general anesthesia. There are a variety of mechanisms involved in the activation of nausea and vomiting. Serotonin, a ubiquitous central and peripheral neurotransmitter, is thought to be the predominant mediator of the perception of nausea and triggering of the vomiting response in both the brain and the periphery via the 5-hydroxytryptamine type 3 (5-HT_3) receptor pathways. 5-HT_3 receptor antagonists disrupt this pathway, largely at the level of the vagal afferent pathways, to decrease nausea and vomiting. This review will focus on dolasetron, an older but sill commonly used 5-HT_3 receptor antagonist and its multimodal mechanism of action, safety and tolerability, patient considerations, and a review of the current literature on its use to combat both chemotherapy-induced and postoperative nausea and vomiting in these two important patient populations.

Keywords: dolasetron, 5-HT_3 antagonists, postoperative, chemotherapy, nausea and vomiting

Background

Over 1.5 million patients are diagnosed with cancer each year in the United States.[1] Many of these individuals will undergo chemotherapy for their disease; however, the consequences and side effects of the treatment are feared by many. Of these side effects, chemotherapy-induced nausea and vomiting (CINV) is one of the most concerning adverse effects for patients initiating treatment, even more so than the associated alopecia.[2] Overall, up to 70%–80% of patients undergoing chemotherapy may experience emesis.[3] CINV may be a precipitating factor in patients abandoning therapy, with a potential negative impact on outcomes.[4] Aside from patient satisfaction, uncontrolled CINV may result in malnutrition, dehydration, weight loss, and electrolyte imbalances, and could lead to several types of complications, such as fractures, esophageal tears, and wound dehiscence.[2,3] Clearly, reduction of this significant side effect improves quality of life for patients undergoing chemotherapy. The knowledge that their adverse effects can be effectively managed may encourage more individuals to undergo therapy and potentially improve their outcomes dramatically.

Likewise, more than 40 million surgeries are performed per year in the United States.[5] Of this large number, nearly one-third of patients experience postoperative nausea and vomiting (PONV).[6] PONV is one of the most commonly reported adverse effects of anesthesia. Even patients with zero known risk factors carry a 10% risk of PONV. This risk increases dramatically to 61% and 79%, respectively, when 3 or 4 risk factors exist (female gender, nonsmoker, history of motion sickness, postoperative

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opioid use, and a history of PONV). Much like CINV, PONV may have significant detrimental effects on surgical outcome, including aspiration, wound dehiscence, and esophageal rupture.[7,8] PONV prophylaxis is an extremely common perioperative practice, even in patients without risk factors for PONV due to the potential adverse outcomes and increased cost of care when PONV is inadequately controlled. 5-Hydroxytryptamine type 3 (5-HT_3) receptor antagonists are generally a mainstay of this practice and are administered many times each day in the operating room.

Serotonin, a ubiquitous central and peripheral neurotransmitter, is thought to be the predominant mediator of the perception of nausea and triggering of the vomiting response in both the brain and the periphery via the 5-HT_3 receptor pathway.[8] Though these receptors are present in the area postrema, which is the chemoreceptor trigger zone for vomiting in the brain, the evidence suggests that the predominant site of action for 5-HT_3 receptor antagonists is in the peripheral vagal afferents (Figure 1). High concentrations of serotonin are found in the enterochromaffin cells of the gut. Toxins, such as chemotherapy, can trigger release of serotonin from these cells, with subsequent activation of 5-HT_3 receptors in vagal afferent pathways which synapse in the nucleus tractus solitarius in the medulla. This, in turn, activates efferent pathways to cause the act of vomiting.[3,8] 5-HT_3 receptor antagonists disrupt this pathway, largely at the afferent vagal level, to decrease nausea and vomiting.[3] This paper will focus on dolasetron, a commonly used 5-HT_3 receptor antagonist, and its multimodal mechanism of action, safety and tolerability, patient considerations, and a review of the current literature on its use to combat both CINV and PONV in these two important patient populations.

Pharmacology and pharmacokinetics of dolasetron

Peripheral serotonin acts on multiple subtypes of 5-HT receptors throughout the peripheral nervous system. The primary serotonin receptor involved in the emesis pathway is the 5-HT_3 receptor.[3] The 5-HT_3 receptor is a ligand-gated ion channel present on the abdominal vagal afferents which, when activated, initiates a cascade of signals throughout the central nervous system to cause the sensation of nausea and the act of vomiting via multiple efferent pathways.[3,9] Dolasetron mesylate is a pseudopelletierine-derived pure 5-HT_3 antagonist which acts to suppress the sensation of nausea and the vomiting response.[8,9] Dolasetron has a short elimination half-life of 0.13–0.24 hours and is rapidly converted by carbonyl reductase to its active form, hydrodolasetron, which has an approximately 50-fold higher affinity for the 5-HT_3 receptor.[7–9] Hydrodolasetron reaches its peak plasma concentration at 0.5–0.6 hours and has a mean plasma elimination half-life of 4–8 hours when administered intravenously. These characteristics give dolasetron an extended duration of action beyond that of ondasetron, the novel 5-HT_3 antagonist. When administered orally, it reaches its peak plasma concentration at one hour and has a plasma elimination half-life of 5–10 hours. Oral bioavailability ranges from 70%–89% depending on increasing age.[9] Hydrodolasetron is predominantly conjugated with glucuronide and/or sulfate groups, as well as

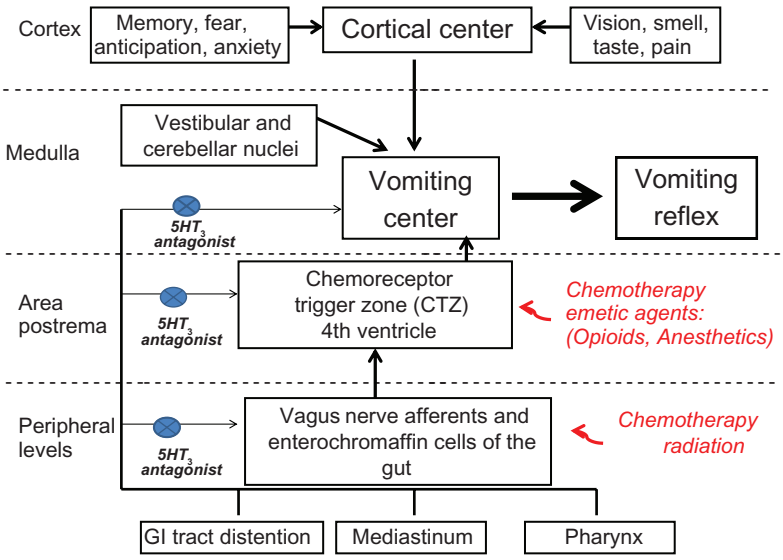

Figure 1 Schematic representation of the mechanisms of emesis associated with chemotherapy-induced and postoperative nausea and vomiting.

oxidated with different forms of cytochrome P450 (CYP). The conjugated forms of hydrodolasetron are then excreted 59% in the urine and 25% in the feces[7,9] (Figure 2).

The metabolism of hydrodolasetron and most other 5-HT_3 receptor antagonists (with the notable exception of granisetron) is, in part, dependent on the CYP2D6 isoform system. Genetic polymorphism in the CYP2D6 isoform system is responsible for alterations in the rates of the metabolism of compounds which are inactivated by this system. This system is responsible for the metabolism of approximately 25% of all prescribed drugs; therefore, these polymorphisms may have a profound clinical impact in certain circumstances. More than 90 distinct alleles have been identified. Carriers of the polymorphic alleles can be classified, based on the metabolic rate of the reference compounds, as extensive metabolizers (wild-type), poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers. These polymorphisms vary by population. For example, up to 10% of Caucasians, but less than 2% of Asians and African-Americans, show the poor metabolizer phenotype. Up to 20% of certain global populations exhibit the ultrarapid metabolizer phenotype. These variants may impact the efficacy of the drugs they metabolize.[7,10]

Dolasetron, for example, may have increased activity and duration of action in the poor metabolizer population, but may have markedly decreased efficacy in the ultrarapid metabolizer population. These polymorphisms could also impact the adverse effects of dolasetron, because these effects have been directly correlated with serum hydrodolasetron levels.[11]

Safety and tolerability of dolasetron

Since the development of the 5-HT_3 receptor antagonists, the overwhelming majority of studies have found them to have a wide margin of safety and to be well tolerated.[7] In fact, the consensus statement on postoperative nausea and vomiting prophylaxis published in 2003 reported that all 5-HT_3 receptor antagonists are "equally safe".[10] The most commonly reported adverse reaction to dolasetron is headache, with an incidence of up to 24%.[9] Other commonly reported events are mild, and include diarrhea, fatigue, and dizziness.[1,3,7,9] However, limited, yet more recently published data suggest there may be evidence of significant cardiovascular events associated with administration of dolasetron.

Early data demonstrated the possibility of prolonged cardiac conduction intervals in both healthy volunteers and perioperative or chemotherapy patients; however, these changes were felt to be transient and not clinically significant.[9] Trigg and Higa most recently published a review of the CINV literature in 2010 and found no or extraordinarily rare adverse cardiovascular events.[1,3] However, there exists some limited evidence that even modest doses of dolasetron can be responsible for significant cardiovascular complications.

Dolasetron has been shown to slow cardiac depolarization by blocking fast sodium channels, thereby reducing maximum upstroke velocity of the action potential.[12–14] This effect causes changes in multiple electrocardiographic parameters, including heart rate, PR interval, QRS duration and, at increased doses (2.4 mg/kg), the QTc interval.[15] There is also evidence to suggest that many drugs, including dolasetron, also interact with potassium channels, thereby affecting repolarization.[16] QTc changes are generally considered to be due to a widened QRS and increases in heart rate; however, there are limited reports of true JT prolongation as well.[11,12,17] These effects have been noted to be directly correlated with the serum hydrodolasetron concentrations and may persist for up to 24 hours (the noted duration of therapeutic effect of a single dose of dolasetron).[11,18,19] A thorough examination of the current literature will show that these reports are limited and similar to other drugs of the class.

Patient considerations regarding dolasetron

Given the aforementioned findings, particular consideration should be given to certain patient populations. Foremost, patients with a pre-existing history of widened QRS or prolonged QTc on electrocardiography should be particularly

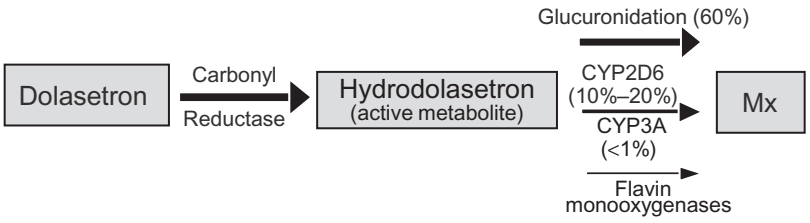

Figure 2 Metabolic pathways of dolasetron.
Abbreviations: CYP2D6, cytochrome P450 2D6 isoform; CYP3A, cytochrome P450 3A isoform; Mx, metabolism.

concerning, especially at the higher doses required for CINV (1.8–2.4 mg/kg). Up to 10%–30% of asymptomatic individuals may have a prolonged QTc at baseline.[20] Likewise, administration of dolasetron in patients known to be predisposed to unstable tachyarrhythmias should also be avoided. However, when choosing a replacement antiemetic, it should be noted that ondansetron has also been shown to induce arrhythmia and prolong QTc, though to a lesser extent than dolasetron.[12,21–23] This is thought to be due to a blockade of potassium channels, which, in turn, prolongs repolarization.[11] Palonosetron has also been shown to prolong QTc by as much as 3.4 msec at doses as low as 0.25 mg.[24] Based on this information, these patients would likely benefit from therapy outside the 5-HT_3 receptor antagonist class.

Genetic variability may also play a role in identifying patients susceptible to significant adverse reactions to dolasetron and other 5-HT_3 receptor antagonists. As previously mentioned, dolasetron is metabolized by the CYP2D6 pathway, which has been shown to exhibit genetic polymorphisms resulting in significant variability in rate of metabolism of substrates.[7] Dolasetron, tropisetron, and palonosetron all share this common pathway, so this variability will not only affect their antiemetic properties, but may also exacerbate the adverse effects of these drugs. However, palonosetron is reported to be unaffected by poor or extensive metabolizers. Granisetron, on the other hand, is metabolized independent of the CYP2D6 pathway, so these polymorphisms do not affect its properties.[10] Recent genetic data has also identified a single nucleotide polymorphism within the *NOS1AP* gene that may place patients at increased risk for developing prolonged QTc after 5-HT_3 receptor antagonist administration.[20] Further investigation into these polymorphisms may allow clinicians to individualize therapeutic regimens more precisely and to treat their patients more effectively. However, dose adjustments for dolasetron are currently unnecessary based on readily available information (age, renal function, and hepatic function).[9]

Renewed clinical data for dolasetron

Studies evaluating dose responsiveness have found a plateaued dose-response curve for PONV. A pooled analysis performed by Philip et al in 2000 demonstrated the dose-response curve plateau well in 1946 postoperative patients. Their results showed that doses greater than 12.5 mg achieved no statistically significant increase in complete response.[25] However, previous data also clearly demonstrate the emetogenic potential of chemotherapy to be much greater than that of PONV, based on dose requirements. In an early review of dolasetron, Balfour and Goa demonstrated a complete suppression of vomiting in 50%–70% of postoperative gynecology patients to doses as low as 12.5–25 mg.[9] However, patients receiving highly or moderately emetogenic chemotherapy require doses as high as 1.8 mg/kg to achieve a complete response (defined as no nausea, emesis, or rescue medication use in the first 24 hours) in 50% and 60%–80% of cases, respectively. An early study by Grote et al compared oral dolasetron doses of 25, 50, 100, and 200 mg, which demonstrated response rates of 44.7%, 71.3%, 73.2%, and 82.5%, respectively.[26] Clearly the plateau effect is far less marked in the setting of moderately emetogenic chemotherapy.[27] Radiation also appears to have a much higher emetogenic potential, because these patients showed complete response after 40 mg of dolasetron.[9]

Many comparative efficacy studies have been published on 5-HT_3 receptor antagonists as each new generation of the class was developed. Most comparative investigations were based on ondansetron, the novel 5-HT_3 receptor antagonist, though there are multiple pharmacologic differences in dolasetron compared with ondansetron. The most clinically notable difference is that the increased elimination half-life of hydrodolasetron, the active metabolite of dolasetron, is 2–3 times greater than for ondasetron. Further, hydrodolasetron has selective affinity for the 5-HT_3 receptor, whereas ondasetron also shows affinity for 5-HT_4, 5-HT_{1B}, 5-HT_{1C}, α_1-adrenergic, and opioid μ receptors.[8] This less selective affinity profile of ondansetron may result in an increased number of adverse or unintended drug reactions, though studies fail to demonstrate this effect clearly. Early results showed that 50 mg doses of dolasetron were as effective in preventing PONV as 4 mg of ondasetron, with 71% and 64% showing a complete response, respectively.[9] However, based on the previously discussed more recent results by Philip et al, these higher doses may have been unnecessary to achieve the same results. Overall, multiple studies have at least demonstrated noninferiority of dolasetron compared with ondansetron.[28–30]

Comparative studies have also been completed against granisetron, another selective 5-HT_3 receptor antagonist. In a small retrospective trial (n = 126), Hamadani et al[2] evaluated antiemetic treatment failure, as defined by nausea or vomiting, in platinum-based chemotherapy comparing dolasetron with granisetron or ondansetron. All 5-HT_3 receptor antagonists were given in conjunction with dexamethasone. In this study, no statistically significant difference in treatment failure was noted, which confirms previously published data demonstrating equivalent efficacy between dolasetron,

granisetron, and ondansetron.[31,32] Therefore, the authors have concluded that the choice of antiemetic should be based on drug cost in the setting of both PONV and CINV.[2,33] Steiner et al also found no clinically or statistically significant difference when granisetron was exchanged for dolasetron in the setting of CINV. This interchange resulted in no difference in patient satisfaction, therapeutic effectiveness, functional status, or nausea severity. However, they did note a substantial cost reduction when using dolasetron.[34] However, when comparing dolasetron 100 mg orally with granisetron 2 mg orally in moderately or highly emetogenic chemotherapy, Tan et al found contradictory results in 2004. Their open-label study of 26 patients demonstrated a complete response rate of 23.1% for the dolasetron group, while the granisetron group showed a complete response in 69.2%. When comparing the cost-effectiveness noted by the previous two authors, Tan et al found a seven-fold increase in rescue medication use in the dolasetron group, which would clearly reduce the cost benefit of dolasetron.[35] However, due to the limited number of patients enrolled in this study and the contradictory results of previously published data, any evidence suggesting the superiority of granisetron over dolasetron is extremely limited.

Most recently, dolasetron has been compared head-to-head with palonosetron, the newest drug of the class, approved by the US Food and Drug Administration in 2008. The earliest study comparing dolasetron with palonosetron was completed by Eisenberg et al in 2003. In this noninferiority study, two doses of palonosetron were compared with dolasetron in 592 patients undergoing moderately emetogenic chemotherapy. At 24 hours after chemotherapy (acute phase CINV), intravenous palonosetron 0.25 mg was found have a higher complete response rate of 63.0% as compared with intravenous dolasetron 100 mg with a 52.9% complete response ($P = 0.049$). Likewise, at 24–120 hours following chemotherapy (delayed CINV), palonosetron remained superior to dolasetron at 48.1% and 36.1%, respectively ($P = 0.018$).[24] In a meta-analysis by Botrel et al in 2011, palonosetron was found to be superior to all other 5-HT_3 receptor antagonists, including dolasetron, in preventing acute-phase and late-phase CINV in moderately or highly emetogenic chemotherapy.[4] In another large, recent study published in 2011, Schwartzberg et al again compared palonosetron with all other 5-HT_3 receptor antagonists in CINV, this time in the setting of triple therapy with dexamethasone and a NK_1 receptor antagonist. In this retrospective study of 4552 patients, palonosetron showed a 17% lower risk of uncontrolled CINV during 5 days of highly emetogenic chemotherapy.[36] Overall, the extremely long elimination half-life of palonosetron (40 hours) appears to give it a therapeutic advantage over dolasetron.[24]

A large area of recent interest in the dolasetron literature is its safety profile. As previously discussed, dolasetron has been shown to slow cardiac depolarization by blocking fast sodium channels, thereby reducing the maximum upstroke velocity of the action potential.[12] This action potential effect causes changes in multiple electrocardiographic parameters, including heart rate, PR interval, QRS duration, and, at increased doses (2.4 mg/kg), the QTc interval. Until recently, these effects were thought to be limited and not clinically significant, with the exception of patients particularly susceptible to these changes (including prolonged QTc at baseline, tachycardia in the setting of acute myocardial infarction).[11] Case reports have been published describing markedly adverse cardiovascular events resulting from both standard doses of dolasetron and intentional overdose. Rochford et al described the dramatic result of a patient ingesting 2000 mg of dolasetron during an intentional overdose. She became markedly hemodynamically unstable, requiring vasopressors, and her electrocardiogram showed sinus rhythm with first-degree atrioventricular block, nonspecific intraventricular conduction delay, and a markedly prolonged QTc of 611 msec.[37] This is obviously an extreme example of the adverse cardiovascular effects of dolasetron, but further significant events have been documented.

Higgins and Bunker have described an episode of intraoperative supraventricular tachycardia immediately following the administration of dolasetron 12.5 mg, a well established acceptable dose for PONV prophylaxis. An otherwise healthy 45-year-old female became hemodynamically unstable requiring treatment with amiodarone. Her symptoms resolved and, interestingly, her postoperative electrocardiogram showed no signs of prolonged intervals.[38] Turner et al have also described an episode of acute QTc prolongation with progression to torsades de pointes and ultimately ventricular fibrillation one hour after dolasetron administration.[39] Clearly, prolongation of QTc has been clearly associated with the development of torsades de pointes and potentially fatal arrhythmia, though only in 1% of these patients overall.[40–42]

Though these are profound examples of the cardiovascular effects of dolasetron, multiple studies consistently support cardiac conduction changes caused by dolasetron, though the clinical relevance of these changes is controversial. However, in 2010, the Food and Drug Administration issued a drug safety communication stating that dolasetron should no

longer be administered intravenously for the prevention of CINV. The basis of this statement is the compelling finding of a dose-dependent prolongation in QT, PR, and QRS intervals in recent studies and a report of a nearly three-fold increase in ventricular arrhythmia in patients treated with dolasetron, compared with ondansetron or granisetron, in one study.[43,44] This, in conjunction with previously documented findings, implies that dolasetron may be proarrhythmic because it prolongs the mean QT/QTc interval by >20 msec.[45] These findings are only applicable to intravenous dolasetron used at the higher doses necessary for CINV, not the decreased dose needed for PONV prophylaxis. However, the Food and Drug Administration issued a similar warning in September 2011 regarding ondansetron for patients with congenital long QT syndrome, which may further the evidence to suggest that this effect is not unique to dolasetron.[46]

Conclusion

Dolasetron represents an older type of $5HT_3$ receptor antagonist. Despite the fact that it has been present on the market for more than 20 years, it is still commonly used for prophylaxis and treatment of both PONV and CINV. Its effectiveness in the treatment of PONV and CINV is similar to other 5-HT_3-antagonists, including ondansetron, topisetron, and granisetron, but it seems to be inferior when compared with newer, longer-acting 5-HT_3-antagonists like palonosetron. The most commonly reported adverse reaction to dolasetron is headache, which is reported in up to 24% of patients. Other commonly reported events are mild, and include diarrhea, fatigue, and dizziness. The newer data provide evidence of significant cardiovascular events, in the form of QTc interval prolongation and subsequent arrhythmia associated with dolasetron administration, particularly in the higher dose ranges. In 2010, the Food and Drug Administration issued a drug safety communication stating that dolasetron should no longer be administered intravenously at higher doses for the prevention of CINV, though similar warnings now exist for ondansetron and granisetron for certain susceptible patient populations. Significant prolongation of the QTc interval seems to be common to all 5-HT_3 antagonists (with the possible exception of palonosetron) and may represent a class effect for this group of drugs.[4] Given the aforementioned findings, particular consideration should be given to certain patient populations prior to the administration of 5-HT_3 receptor antagonists. Foremost, patients with a pre-existing history of widened QRS or prolonged QTc on electrocardiogram should be particularly concerning, especially at the higher doses required for CINV.

Disclosure

The authors report no conflicts of interest in this work.

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