The Cardiototoxic Potential of the 5-HT_{3} Receptor Antagonist Antiemetics: Is There Cause for Concern?

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ABSTRACT
Purpose. To review and evaluate the potential cardiac effects of 5-HT_{3} antiemetic treatment in patients who may be predisposed to cardiac complications resulting from malignancy, cytotoxic oncologic regimens, or preexisting comorbid conditions.

Design. A literature review was conducted on the negative cardiovascular effects of chemotherapeutic agents, and, more specifically, on the cardiac interactions of the 5-HT_{3} receptor antagonists commonly used to treat chemotherapy-induced nausea and vomiting.

Results. Clinical studies in healthy subjects have reported electrocardiograph changes following administration of 5-HT_{3} receptor antagonists. However, there are limited data on the use of 5-HT_{3} antiemetics when administered with cardiotoxic chemotherapy. Nonetheless, the development of significant electrocardiograph changes with some agents may indicate a potential for significant cardiac effects in patients, particularly those who may be predisposed to cardiac complication.

Conclusions. As the predicted human life span increases, clinicians will be treating a larger, older oncology population. Because two of the most common major comorbidities are cardiovascular related, we need to be acutely aware of the toxic effects of chemotherapy, as well as the possible cardiac interaction of supportive agents, specifically the 5-HT_{3} antiemetics. Until more data are made available, the best antiemetic option for patients receiving emetogenic and cardiotoxic chemotherapy may be the agent with the fewest apparent cardiac effects.

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INTRODUCTION
Cardiac disease in cancer patients can be a preexisting comorbid condition, develop during cytotoxic treatment with cardiotoxic regimens, or, occasionally, result from the malignancy. Administration of cardiotoxic chemotherapy to patients with preexisting cardiac disease can be a major challenge for clinicians when attempting to balance potentially curative therapy for the cancer with the consequences of exacerbating the cardiac disease. Agents for supportive care, e.g., the antiemetic 5-HT_{3} receptor antagonists, must also be considered when evaluating adverse cardiac effects, as measurable electrocardiographic (ECG) changes have been reported despite their overall excellent safety profile [1-7].

While usually benign, the effects of the 5-HT_{3} receptor antagonists on cardiac function in patients with preexisting cardiovascular comorbidities and/or who are receiving potentially cardiotoxic chemotherapies have not been addressed. Although the clinical consequences in practice are relatively negligible, it is important to know the effect that the different 5-HT_{3} receptor antagonists may have on cardiac function in order to successfully manage a patient with cancer and cardiac disease, or potential chemotherapy-induced cardiac toxicity.

COMORBID CARDIAC DISEASE
Over 1.2 million patients are diagnosed with cancer in the United States each year, with over half of these (61%) aged 65 years and older [8]. As our predicted life span increases, clinicians will be dealing with an increasingly larger, older oncology population that is more likely to have concomitant health conditions. As the cardiovascular system ages, it undergoes various morphologic changes that may lead to the eventual development of cardiac cellular hypertrophy, myocardial ischemia, and increased vulnerability to induced apoptosis. Prospective [9] and retrospective [10] studies have demonstrated a high incidence of comorbid conditions in...
older patients with cancer. An assessment of 7,600 cancer patients at least 55 years old found that the two most common major comorbidities were hypertension (43%) and heart-related conditions (39%) [11].

**Cardiotoxic Chemotherapy**

Epirubicin, doxorubicin, daunorubicin, and idarubicin belong to the group of chemotherapeutic agents classified as anthracyclines, with activity against a variety of malignancies including breast and lung cancer. This class of agents is well known for cardiac toxicity that may manifest as acute episodes of ECG disturbances, myocarditis-pericarditis, congestive heart failure (CHF), or cumulative dose-related cardiomyopathy [12, 13]. Contributing risk factors for cardiac toxicity are gender, increased cumulative dose, age, mediastinal or cardiac irradiation, prior anthracycline exposure, a history of cardiac disease, and method of administration [12, 14-17]. Breast cancer patients frequently receive anthracyclines as a component of standard combination chemotherapy [18]. When paclitaxel became available, the drug was studied in combination with other chemotherapy agents, including doxorubicin [19-23]. A sequence-dependent pharmacokinetic interaction between doxorubicin and paclitaxel has been reported in patients treated for metastatic breast cancer [22].

Among the other chemotherapeutic agents reported to have negative cardiovascular effects are fluorouracil, high-dose cyclophosphamide, and interleukin-2 (IL-2). Fluorouracil administration has been associated with angina and myocardial infarction (MI), and with ventricular arrhythmias due to coronary spasm [15, 24, 25], whereas cyclophosphamide, at doses greater than 120 mg/kg, can cause fatal hemorrhagic myocardial necrosis [15]. A dose-dependent cardiotoxicity secondary to cyclophosphamide use in bone marrow transplantation manifests as a decrease in ECG voltage and an increase in left ventricular mass [26]. In patients treated with IL-2, 1% to 4% experience supraventricular and ventricular arrhythmias, myocarditis, ischemia, and MI [27].

The anthracyclines, fluorouracil, and high-dose cyclophosphamide not only potentiate cardiotoxicity, they also cause nausea and vomiting. Patients who receive these chemotherapy agents usually receive prophylactic antiemetics, and these are often one of the 5-HT3 receptor antagonists. When these agents are administered concomitantly with a potentially cardiotoxic chemotherapy agent, and/or to patients with preexisting cardiac disease, is there cause for concern?

**Cardiac Effects of the 5-HT3 Receptor Antagonist Antiemetics**

Good control of chemotherapy-induced nausea and vomiting has been achieved with the development and clinical use of the 5-HT3 receptor antagonists. Chemotherapy-induced vomiting results from the neural stimulus of the vagal and sympathetic fibers via the spinal cord to distinct areas in the brain that control vomiting [28]. Chemotherapy, particularly at high doses, initiates vomiting by releasing large amounts of serotonin (5-HT3), which stimulates the receptors on vagal abdominal afferent fibers in the gastrointestinal tract [29]. The heart, however, also has vagal innervation and there may be a potential for cardiac interaction when these agents are administered [30].

Ondansetron (Zofran®; GlaxoSmithKline; Philadelphia, PA), granisetron (Kytril®; Roche Laboratories; Nutley, NJ), and dolasetron (Anzemet®; Hoechst Marion Roussel, Inc; Kansas City, MO) are the three 5-HT3 receptor antagonists currently available in the U.S. These agents are effective and generally well tolerated; not all 5-HT3 receptor antagonists are the same, however, especially with regard to effects on the myocardium. Of those agents currently available, only dolasetron labeling carries a warning that ECG interval changes (PR, QTc, and JT prolongation, plus QRS widening) can occur. The active metabolites of dolasetron may block sodium channels, independent of their 5-HT3 receptor-blocking activity [31].

**Effects of 5-HT3 Receptor Antagonists in Healthy Adults**

Clinical trials in healthy subjects have demonstrated ECG changes following administration of 5-HT3 receptor antagonists (Table 1). Dolasetron in doses ranging from 0.6 to 5.0 mg/kg was administered i.v. to 80 healthy male volunteers [32]. Results showed transient and asymptomatic ECG changes that included small mean increases in PR interval and QRS complex duration versus baseline. At doses greater than 3 mg/kg (recommended clinical dose is 1.8 mg/kg), there were small increases in mean PR interval and QRS duration accompanied by small increases in heart rate or QTc. In addition, seven subjects experienced asymptomatic, treatment-emergent intraventricular conduction defects (QRS duration ≥100 msec) 1 to 2 hours after infusion of doses ≥3 mg/kg, which resolved by the end of the study period.

The cardiovascular effects of a 2-mg oral dose of granisetron were monitored in a study of nine healthy subjects [33]. No sustained arrhythmias were recorded on ambulatory monitoring for a mean 21.6 hours, including a 3-hour period of submaximal exercise in a 40°C environment. It was concluded that granisetron lacked proarrhythmic activity.
The cardiac effects of ondansetron were compared with those of dolasetron and granisetron in two separate trials [5, 6]. Thirty healthy male subjects each received single i.v. doses of ondansetron (32 mg), dolasetron (1.2, 1.8, 2.4 mg/kg), and placebo [5]. Compared with placebo, each dose of dolasetron administered caused a significant increase in one or more ECG measurements within 4 hours of administration. These significant increases were produced by dolasetron in the following ECG measurements: PR, QRS (p < 0.001), and QTc (p < 0.01) at a dose of 1.2 mg/kg; PR, QRS, QTc, and heart rate (p < 0.001) at a dose of 1.8 mg/kg; and PR, QRS, QTc (p < 0.001), heart rate (p < 0.01), and QT (p < 0.05) at a dose of 2.4 mg/kg. The increase in heart rate with dolasetron 2.4 mg/kg demonstrated a significant dose-related trend (p < 0.01), with a mean increase ≤3 beats/minute. Ondansetron produced a decreased heart rate (mean decrease ≤2 beats/minute; p = 0.033) and a statistically significant increase (p < 0.0048) in JT interval, but no significant change in QTc. Compared with placebo, ondansetron also significantly increased the QT interval (p < 0.01).

A placebo-controlled trial compared the cardiovascular effects of ondansetron with those of granisetron in 13 healthy adults without significant abnormalities in resting 12-lead ECG and a heart rate >45 beats/minute [6]. Granisetron 10 µg/kg was administered i.v. over 5 minutes or 30 seconds, and ondansetron 32 mg was administered i.v. over 15 minutes. Granisetron was associated with less effect on ECG than ondansetron. There were no significant changes in the QTc interval between the two administration protocols for granisetron, or among the granisetron groups and placebo. The mean postdose QTc interval was longer for ondansetron when compared with placebo and with granisetron for all 12 subjects.

**Cardiac Effects of 5-HT3 Receptor Antagonists in Cancer Patients**

**Noncomparative Studies**

Table 2 summarizes cardiac effects reported with 5-HT3 receptor antagonists in patients receiving chemotherapy. To date, only one study has focused specifically on the cardiac effects of a 5-HT3 receptor antagonist when used with cardiotoxic chemotherapy [34]. This study investigated the cardiac effects of a single 3-mg i.v. infusion of granisetron, followed by administration of doxorubicin (median dose 40 mg/m²; range 20-100 mg/m²) or epirubicin (median dose 40 mg/m²; range 10-50 mg/m²) in 30 cancer patients. The ECG tracings were taken prior to granisetron administration, immediately after, and 5 to 10 minutes postchemotherapy infusion. All patients were observed for at least 2 hours. Patients were excluded if they had angina, an unstable heart rhythm, or clinical symptoms of CHF, although they were not excluded if they had received previous chemotherapy. Subsequent ECG tracings showed asymptomatic increases in the PR interval (p < 0.02) that remained within normal limits. There were no statistically significant changes in the QRS duration, cardiac rhythm, or the QTc intervals. Minor changes in the PR interval were not deemed clinically important.

After administration of i.v. granisetron at five times the labeled United States dose (50 µg/kg), cardiac effects were reported in a small study of 12 patients who received chemotherapy for bone and soft-tissue sarcomas [30]. Four patients had ECG changes in 12 of 72 courses of repeat chemotherapy regimens consisting of high-dose methotrexate, vincristine, cisplatin, pirarubicin, bleomycin, ifosfamide, or actinomycin D. No patient reported chest pain, although one

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### Table 1. Cardiac effects of the 5-HT3 receptor antagonists in healthy subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Cardiac effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hunt et al.</em></td>
<td>Dolasetron 0.6-5.0 mg/kg i.v</td>
<td>Increased PR interval and QRS complex duration versus baseline. Increased heart rate at ≥3 mg/kg.</td>
</tr>
<tr>
<td><em>Gray et al.</em></td>
<td>Granisetron 2 mg oral</td>
<td>Lacked proarrhythmic activity.</td>
</tr>
<tr>
<td><em>Benedict et al.</em></td>
<td>Dolasetron 1.2, 1.8, 2.4 mg/kg i.v, Ondansetron 32 mg i.v</td>
<td>Increase in PR, QRS, and QTc intervalsa and increased heart rate with dolasetron. Decreased heart rateb and increased JT intervalc with ondansetron. Both agents increased QT intervald.</td>
</tr>
<tr>
<td><em>Boike et al.</em></td>
<td>Granisetron 10 µg/kg i.v, Ondansetron 32 mg i.v</td>
<td>Ondansetron had a statistically longer QTc interval.</td>
</tr>
</tbody>
</table>

Note: 

- a p < 0.001; b p = 0.033; c p < 0.0048; d p < 0.01 and p < 0.05 for ondansetron and dolasetron, respectively.
patient reported chest pressure. It should be noted that cardiac function and timing of ECG changes in relation to granisetron administration were generally unreported. It is difficult to compare results of this study with those of other studies because of multiple chemotherapy agents and the high dose of granisetron employed.

Cardiac effects following dolasetron therapy were observed in two clinical studies that specifically excluded patients with preexisting cardiomyopathy, CHF, complete bundle branch block, ≥1st heart block, or arrhythmias requiring medication [7, 35]. Both studies evaluated escalating doses (25, 50, 100, or 200 mg) of oral dolasetron. In one study, eligible patients received carboplatin (275 to 400 mg/m²; n = 184) or cisplatin (20 to 50 mg/m²; n = 123) as their primary chemotherapeutic agent; 29 patients also received fluorouracil, and 38 also received cyclophosphamide [7]. Statistically significant (p < 0.001) linear trends for increased PR, QTc, and QRS intervals on ECG tracings were reported with increasing dolasetron dose. These transient changes occurred at 1 to 2 hours post-therapy and appeared related to plasma concentrations of the major metabolite of dolasetron. A similar study of oral dolasetron (n = 319) repeated these results in patients who received doxorubicin (≥40 mg/m² alone or 25-75 mg/m² with cyclophosphamide) or cyclophosphamide (500 to 1,200 mg/m²) as the primary chemotherapeutic agent [35]. The changes resolved within 24 hours and were not considered clinically relevant.

There are seven case reports that associate i.v. ondansetron (10 mg × 3, 15 mg once and × 2, and 30 mg × 3) with chest pain in patients aged 60 to 78 years [1]. Two of these patients had received potentially cardiotoxic chemotherapy, fluorouracil, and/or doxorubicin. In three patients, pain did not recur with a change in antiemetics. These cases do not prove an association between ondansetron and angina, but the authors reported that after the first four patients, two of whom suffered cardiac arrest (one death) and one who died of MI,
they discontinued ondansetron at the first sign of chest pain.

**Comparative Studies**

Adverse cardiac events have been reported in comparative studies of the efficacy of 5-HT₃ receptor antagonists. In a study of single-dose i.v. dolasetron (1.8 mg/kg, n = 198; or 2.4 mg/kg, n = 205) versus i.v. ondansetron (32 mg, n = 206) for acute cisplatin-induced emesis, patients were excluded if they had a history of CHF, antiarrhythmic medication, preexisting complete bundle branch block, cardiomyopathy, or >1º heart block [36]. Asymptomatic prolongation for the PR, QRS, QT, QTc, and JT intervals was recorded on ECG with both agents. The results of this study reported that the average changes from baseline in PR, QRS, and QTc intervals at 1 to 2 hours were greater for dolasetron compared with ondansetron.

A phase III study of 696 patients compared the efficacy and safety of dolasetron (2.4 mg/kg i.v. followed by 200 mg orally) with ondansetron (32 mg i.v. or 8 mg orally twice daily) in patients treated with moderately emetogenic chemotherapy that included doxorubicin, epirubicin, cisplatin, carboplatin, and cyclophosphamide [37]. Patients were excluded for clinically significant cardiac, hepatic, or renal disease. Asymptomatic ECG changes were recorded in both treatment groups. Prolongation of the QTc developed in 41% of dolasetron-treated and 19% of ondansetron-treated patients. QRS prolongation was reported in 24% and 9% of dolasetron- and ondansetron-treated patients, respectively.

In patients receiving cisplatin (≤100 mg/m²), administration of a single dose of i.v. ondansetron (32 mg, n = 25) or i.v. dolasetron (2.4 mg/kg, n = 20) resulted in asymptomatic, reversible ECG interval prolongation for PR, QRS, QT, and QTc 2 hours postantiemetic therapy [3]. Increases in PR, QRS, and QT after both agents, and QTc after dolasetron were significant (p < 0.05). In addition, ondansetron significantly slowed heart rate a mean 8 beats/min (p < 0.05). Changes detected by ECG and heart rate resolved within 24 hours.

A multicenter, randomized, double-blind, double-dummy trial was designed to compare i.v. dolasetron (1.8 or 2.4 mg/kg) with i.v. granisetron (3 mg) for the treatment of emesis from high-dose cisplatin (>80 mg/m²) [4]. Exclusion criteria were a CHF history, arrhythmias requiring medication, >1º heart block, cumulative cardiotoxicity secondary to anthracyclines or anthracenediones, and abnormal serum levels of potassium or calcium. Patients who received dolasetron (n = 324) had significantly greater increases in QTc interval (p = 0.0016), and PR interval (p = 0.0002) at 1-2 hours post-treatment than those who received granisetron (n = 150). The ECG changes in any of the treatment groups did not result in clinical symptoms, and vital signs showed no evidence of an effect.

**Drug Interactions**

The effects of the 5-HT₃ receptor antagonists on the pharmacokinetics and pharmacodynamics of other drugs commonly administered to patients with cancer have been studied, as well as the effects of some of those drugs on the 5-HT₃ agents. There are two historical studies that suggest that ondansetron may lower the area under the curve of high-dose cyclophosphamide by about 15% [38, 39], but neither of these was a clinical trial. In the first of these studies, cisplatin AUC was also decreased [38], but it was 10% higher in the other [39]. Ondansetron did not alter the pharmacokinetics or pharmacodynamics of temazepam in a randomized clinical trial conducted in 24 normal volunteers [40], nor did it alter the analgesic effect of alfentanil [41]. Cisplatin and 5-fluorouracil were found to have no effect on the pharmacokinetics of oral or i.v. ondansetron in a clinical trial in cancer patients [42].

Atenolol decreased the clearance of hydrodolasetron by about 27% [31]. Furosemide, nifedipine, diltiazem, angiotension-converting enzyme inhibitors, verapamil, glyburide, and propranolol are reported to have no effect on the clearance of hydrodolasetron [31]. However, any drug that lengthens the QT interval or causes hypokalemia or hypomagnesemia would be expected to have a pharmacodynamic interaction with hydrodolasetron. This would be expected to be particularly severe for quinidine that is also a potent inhibitor of CYP2D6 [43], which contributes to the metabolism of hydrodolasetron. Other drugs with a potential pharmacodynamic interaction with dolasetron are tricyclic antidepressants, cisapride, pentamidine, amphotericin (potassium depletion), and diuretics. Patients with cardiomyopathies induced by the anthracyclines or underlying coronary disease are also more vulnerable to arrhythmias and may be at increased risk, so caution is advised.

**DISCUSSION**

Oncology patients may have a variety of comorbid diseases as a result of age, cancer stage, and the extent of previous chemotherapy. Cancer is most prevalent in people over 65 years of age, and this population has had more exposure time to cardiotoxins, acquired diseases, the onset of cardiovascular disease [12], and the progressive myocyte hypertrophy and cell loss associated with aging, which may predispose them to the cardiotoxic effects of chemotherapy [44]. In addition, electrolyte disturbances, cytotoxins, radiation therapy, vomiting, and malnutrition may also adversely affect the heart [45-49]. Cardiac complications directly attributed to malignancy include metastases to cardiac struc-
turers, carcinoid heart disease, and dysrhythmias [46, 50]. In general, the contribution of underlying conditions to cardiac risk is supported by evidence that older age, previous cardiac disease, or hypertension have been shown to increase the risk for doxorubicin-induced cardiotoxicity [12, 51-53].

The presence of comorbid heart disease in cancer patients is especially challenging because of the known cardiotoxicity of effective chemotherapy regimens. The anthracyclines, combination treatment with doxorubicin and paclitaxel, fluorouracil, high-dose cyclophosphamide, and IL-2 are all known to have cardiotoxic side effects.

Doxorubicin is perhaps the most studied of the anthracyclines in regard to anthracycline-induced cardiotoxicity. Cardiotoxicity induced by doxorubicin is related primarily to the cumulative dose, and can have either an early or late onset [12, 54]. At cumulative doxorubicin doses greater than 450 to 500 mg/m², 7% to 15% of patients developed CHF [14]. Early-onset cardiotoxicity is characterized by the acute development of arrhythmias, such as ventricular and supraventricular tachycardia, and left ventricular dysfunction during or after administration. Chronically progressive cardiotoxicity usually occurs within 1 year of administration [12, 16], but can be a late complication [55, 56]. Breast cancer patients frequently receive anthracyclines as a component of standard combination chemotherapy [18]. In clinical trials of breast cancer patients, cardiotoxicity was shown to increase with increasing dose per cycle [17] and increasing cycles [57]. Age also plays a role in increasing the potential for cardiotoxicity in breast cancer patients, as most breast cancer is diagnosed in women older than 65 years [8]. Doxorubicin is also a standard component in regimens for lung cancer. As with breast cancer, the majority of lung cancers are diagnosed in patients older than 65 years. An additional complication with lung cancer is cardiac disease as a result of compromised lung function.

Reports of significant bradyarrhythmias and atrioventricular conduction disturbances associated with paclitaxel alone have been rare, with the exception of sinus bradycardia [58]. A few cases of CHF, some fatal, have been precipitated by paclitaxel in patients who had previously received anthracyclines or mitoxantrone [34, 59]. A sequence-dependent pharmacokinetic interaction between doxorubicin and paclitaxel has been reported [22], and initial studies of a paclitaxel/doxorubicin combination regimen in metastatic breast cancer showed that paclitaxel may exacerbate doxorubicin-induced cardiotoxicity [19, 20]. A phase I study of patients with metastatic breast cancer demonstrated that paclitaxel administered before doxorubicin increased mean plasma doxorubicin concentrations (Cmax) by 70% at the end of infusion compared with the same dosages administered in reverse sequence [22]. This interaction and increase in doxorubicin Cmax by paclitaxel could increase cardiac toxicity. A study in breast cancer patients evaluated the potential for cardiac toxicity with a doxorubicin/paclitaxel/cyclophosphamide combination administered in nine sequential cycles [23]. Results demonstrated that the sequential administration of these agents in different cycles did not increase the risk of cardiac toxicity.

Therapy may be further complicated by possible drug interactions and cardiac adverse events associated with agents administered for supportive care. This review has explored the extent of cardiac effects mitigated by the popular and effective 5-HT3 receptor antagonists that are administered to prevent chemotherapy-induced nausea and vomiting. Published literature specifically reporting cardiac effects of the 5-HT3 receptor antagonists is limited. Small sample sizes, differences in exclusion criteria, and the use of different chemotherapy regimens confound literature analysis, and the majority of available data are from studies that investigated efficacy and simply documented the occurrence of cardiovascular effects.

Is there cause for concern when using a 5-HT3 receptor antagonist with potentially cardiotoxic chemotherapy and/or in patients with preexisting cardiac disease? Although available data fail to show a clinically significant cardiac effect with the 5-HT3 receptor antagonists, the development of significant ECG changes in healthy subjects for some agents, particularly the increased QTc with dolasetron, may indicate a potential for significant cardiac effects in predisposed individuals. Other drugs that lengthen the QT interval have been associated with arrhythmias, particularly “torsade des pointes.” In fact, the European Agency for the Evaluation of Medicinal Products proposed that all noncardiac drug candidates be studied for their potential to induce QTc prolongation [60].

The available comparative studies of 5-HT3 receptor antagonists report that ondansetron has a greater effect on ECG intervals compared with granisetron, and that dolasetron has a greater effect on ECG intervals compared with ondansetron or granisetron. Overall, the total number of patients in these clinical studies is small. Until larger and more inclusive comparative studies are conducted, the best antiemetic option for patients receiving emetogenic and cardiotoxic chemotherapy is the agent with the least apparent cardiac effects.

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