An Evaluation of Potential Signals for Ventricular Arrhythmia and Cardiac Arrest with Dolasetron, Ondansetron, and Granisetron in the FDA Combined Spontaneous Reporting System/Adverse Event Reporting System

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ABSTRACT

Background: Of the US Food and Drug Administration (FDA)-approved 5-hydroxytryptamine type 3 (5-HT₃)-receptor antagonists, dolasetron, ondansetron, granisetron, and palonosetron, only dolasetron and palonosetron have a precaution in their FDA labeling concerning corrected QT interval (QTc) prolongation. At FDA-approved doses, QTc prolongation has been observed in clinical trials with some 5-HT₃-receptor antagonists (however, palonosetron has been only recently approved, with few published clinical data available). However, due to patient exclusion criteria, such trials with 5-HT₃-receptor antagonists may have failed to examine the risk of these agents in “real world” patients with cancer.

Objective: The aim of this analysis was to assess the potential risk for selected cardiac adverse events associated with dolasetron, ondansetron, and granisetron use.

Methods: The FDA combined Spontaneous Reporting System/Adverse Event Reporting System database was analyzed. The process of analyzing such a database for early warnings of potential hazards is known as signal generation. The statistical technique proportional reporting ratio (PRR) was used to aid detection of a potential signal within the database. PRR is the observed proportion of a given adverse event for the drug of interest (the number of events of interest for the drug divided by the total number of reports for the drug) divided by the expected proportion. Through the third quarter of 2002, the database was searched using the preferred term electrocardiogram qt corrected interval prolonged.

Results: One, 3, and 0 cases were reported for dolasetron, ondansetron, and granisetron, respectively. The number of cases did not satisfy 1 of the 3 criteria we utilized to define a potential signal, the 3 criteria being: 3 or more reported cases of the adverse event, a PRR value of at least 2, and a χ² value of >4. As this term may be unlikely to be reported, the database was also searched using the term ventricular arrhythmias and cardiac arrest. The PRR, used as a parameter
to detect a potential signal within the database, was 3.23, 1.31, and 1.13 for dolasetron, ondansetron, and granisetron, respectively. The number of observed ventricular arrhythmias and cardiac arrests was -3-fold higher with dolasetron compared with the expected value (calculated by dividing the individual agent’s total number of events reported by the proportion of adverse events for all agents combined). The results for dolasetron fulfilled the criteria we used to define a potential signal.

Conclusions: This analysis detected a potential signal for ventricular arrhythmias and cardiac arrest with dolasetron, but not with ondansetron or granisetron. However, there are limitations of a PRR analysis, which include only measuring cases that have been reported, providing relative frequencies instead of actual rates, and not providing information on the severity of adverse events or causal relationships. In addition, our analysis does not include consideration of concomitant medications, and only 2 search terms were used. Errors in identifying potential signals may also include confounding factors, such as the underlying disease, potential confusion with reporting under trade and generic names, and potential multiple reporting of the same case. (Curr Ther Res Clin Exp. 2005;66:409-419) Copyright © 2005 Excerpta Medica, Inc.

Key words: antiemetic, 5-hydroxytryptamine type 3 antagonists, cardiovascular events.

INTRODUCTION

The electrocardiogram (ECG) QT interval is often transformed (normalized) into a heart rate-independent “corrected” value known as the corrected QT (QTc) interval. Prolongation of the cardiac QTc interval is a risk factor for sudden cardiac death and torsades de pointes, a potentially fatal cardiac arrhythmia. A cutoff value of 440 ms for QTc prolongation is the generally used value in international literature.

Cardiac sodium and potassium channels are both important determinants of the ECG. Of the 5-hydroxytryptamine type 3 (5-HT₃)–receptor antagonists approved by the US Food and Drug Administration (FDA) for use in prophylaxis of chemotherapy-induced nausea and vomiting, dolasetron, ondansetron, and granisetron have the ability to block these cardiac sodium and potassium channels in vitro with varying potency. Palonosetron, another agent approved by the FDA, has not been tested in this in vitro model.

Clinical reports have demonstrated that dolasetron use is associated with prolongation of the QTc interval, and, although rare, certain studies have also associated ondansetron use with QTc interval prolongation. Nonetheless, these changes with both dolasetron and ondansetron were considered clinically insignificant by the study investigators. The ECG interval prolongations, including QTc interval, observed following the administration of ondansetron 32 mg IV in patients receiving cisplatin-based chemotherapy were clinically asymptomatic, and the incidence of cardiovascular adverse events that
might be deemed related to these ECG changes was low.4 Similarly, the QTc interval prolongation observed in patients treated with ondansetron 32 mg IV or 8 mg PO BID following moderately emetogenic chemotherapy was also asymptomatic and did not require treatment.12 Although use of ondansetron 32 mg IV was associated with a significantly longer postdose QTc interval compared with either vehicle or granisetron 10 µg/kg IV regimens in healthy adults, these changes were transient and not associated with clinical symptoms.17 Granisetron use does not appear to significantly prolong the QTc interval.7,17-25 One study has reported some ECG changes associated with the use of granisetron 50 µg/kg IV in patients undergoing repeat courses of chemotherapy with multiple chemotherapy agents.26 However, there were no reports of QTc interval prolongation, and the authors did not conclude that granisetron had a clinically significant effect on the heart.

The effects of dolasetron, ondansetron, and granisetron use on the QTc interval have been compared in some clinical trials.7,12,17 Dolasetron (1.8 or 2.4 mg/kg IV) has been reported to produce a significantly greater increase in QTc interval prolongation compared with granisetron (3 mg IV)7 and ondansetron (32 mg IV or 8 mg PO BID)12 in patients with cancer. Furthermore, another vehicle-controlled study has demonstrated that the use of IV ondansetron (32 mg infused over 15 minutes) is associated with a statistically longer postdose QTc interval compared with 2 IV granisetron regimens (10 µg/kg infused over 5 minutes or 30 seconds); however, the magnitudes of the prolongations were deemed unlikely to be clinically meaningful.17 However, even clinically insignificant prolongations may be important in patients who already have borderline or slight prolongation of their QT interval.

Dolasetron carries precaution in its labeling concerning dose-dependent QTc prolongation and other ECG interval effects,27 urging caution in patients who have or may develop prolongation of cardiac conduction intervals, whereas the labels of ondansetron28 and granisetron29 do not contain a precautionary statement about QTc prolongation.

Some of these clinical studies were performed in healthy volunteers5,6,8,9,15–17,19,20 or in patient populations that exclude elderly oncology patients and/or those with certain cardiac comorbidities4,7,10–14,18,21,23,24 or receiving certain antiarrhythmic medications.4,7,10,11,21 Thus, it is postulated that these trials did not assess the true risk of these agents in “real world” patients with cancer, who are often older than 65 years, have comorbidities, and/or are taking multiple medications.30–32 Therefore, the objective of this analysis was to assess the risk for selected adverse cardiac events associated with the use of the 5-HT₃-receptor antagonists dolasetron, ondansetron, and granisetron in patients in the FDA combined Spontaneous Reporting System and Adverse Event Reporting System (SRS/AERS) database.33 The database originates from 1969 and comprises adverse events reported by health professionals and drug manufacturers, who are required by regulation to forward adverse event reports to the FDA.
MATERIALS AND METHODS

Through the third quarter of 2002, the FDA SRS/AERS database was searched using the preferred term electrocardiogram qt corrected interval prolonged for reports associated with dolasetron, ondansetron, or granisetron use. The high-level term ventricular arrhythmias and cardiac arrest was also used to search the database through the third quarter of 2002, as described in the results below. The starting null hypothesis was that the 3 agents would have an equal proportion of these adverse events in their event profiles.

The process of analyzing spontaneous adverse drug reaction reports for early warnings of potential hazards is known as signal generation. Generation of a potential signal may be a starting point for further investigation. However, the question of what constitutes a signal requires certain judgments to be made, such as on the number and quality of case reports. The use of statistical analyses may aid this judgment process. In this study, a proportional reporting ratio (PRR) was used to aid detection of a potential signal within the database. This statistical technique has been used previously to aid detection of signals from spontaneous adverse drug reaction reports. The PRR is the observed proportion of a given adverse event for the drug of interest (the number of events of interest for the drug divided by the total number of reports for the drug) divided by the expected proportion. The expected proportion is based on a null hypothesis that predicts no relationship between the drug of interest and the adverse event (eg, ventricular arrhythmias and cardiac arrest), in which case, the proportion of such adverse events for the drug of interest (within its total adverse event profile) would be the same as that for all drugs in the database combined. Therefore, the expected proportion is the number of events of interest for all other drugs divided by the total number of reports for all other drugs. The null value for a PRR is therefore 1, as the proportion of observed and expected adverse events should be equal.

A previous study using the PRR as a tool for analysis stated that 3 criteria be used to indicate a potential signal. We have adopted the same criteria to indicate the presence of a potential signal for dolasetron, ondansetron, or granisetron. In this analysis of the FDA SRS/AERS database, the 3 criteria needed to be present to constitute a potential signal (and therefore a potential association between the drug of interest and the adverse event) were:

- Three or more reported cases of the adverse event;
- A PRR value of at least 2; and
- A $\chi^2$ value (the associated statistic for this type of analysis) of >4.

The PRR for this analysis was calculated using QScan version 2.0 (QED Solutions Inc., Houston, Texas).

RESULTS

The original search term revealed that 1, 3, and 0 cases of electrocardiogram qt corrected interval prolonged were reported to the FDA SRS/AERS database for
dolasetron, ondansetron, and granisetron, respectively. This yielded a PRR of 4.97 for dolasetron, 1.42 for ondansetron, and 0.00 for granisetron. The number of cases revealed did not therefore fulfill the signal criteria regarding minimum number of reported cases (at least 3) and was too few to evaluate for a potential signal with this search term. 34

Ambulatory patients with cancer rarely undergo routine ECG monitoring. It was thus deemed unlikely that this original search term would be reported as an adverse event of therapy with dolasetron, ondansetron, or granisetron. The high-level term ventricular arrhythmias and cardiac arrest was therefore used as a surrogate to search the database through the third quarter of 2002. The number of observed ventricular arrhythmias and cardiac arrest events was ~3-fold higher with dolasetron compared with expected (Table). Using the 3 criteria of Evans et al34 as an indication of a signal, a potential signal for ventricular arrhythmias and cardiac arrest events was detected with dolasetron, but not with either ondansetron or granisetron. 34 For dolasetron, all 3 criteria for a potential signal were fulfilled: the number of reported cases of the adverse event was at least 3, the PRR value was at least 2, and the $\chi^2$ value was >4 (Table). The 3 criteria were not fulfilled for either ondansetron or granisetron.

**DISCUSSION**

To determine selected cardiac adverse events associated with the use of the 5-HT3-receptor antagonists dolasetron, ondansetron, and granisetron, the FDA SRS/AERS database was searched. A PRR is meant to facilitate the early detection of safety signals and is used for hypothesis generation. As a means of analysis, the PRR has some limitations. Specifically, it measures only cases that have been reported, it provides relative frequencies instead of actual rates, and it does not provide information concerning the severity of adverse events or causal relationships. Additional limitations of our analysis include that concomitant med-

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<th>Drug</th>
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PRR = proportional reporting ratio.

*Calculated using QScan version 2.0 (QED Solutions Inc., Houston, Texas).
ications were not taken into account, and only 2 search terms were used. Errors in identifying potential signals may also include confounding factors, such as the underlying disease, potential confusion with reporting under trade and generic names, and potential multiple reporting of the same case. Such limitations necessitate interpretation of the results with caution, but do suggest a need for further research into the potential signal for ventricular arrhythmias and cardiac arrest with dolasetron.

The analysis revealed a potential signal for ventricular arrhythmias and cardiac arrest with dolasetron, but not with either ondansetron or granisetron. A possible explanation for our findings may be the differential sodium channel blockade by these drugs. Drugs that block sodium channels may produce widening of the QRS interval (the phase of the ECG representing ventricular depolarization), possibly resulting in ventricular arrhythmias. The active metabolites of dolasetron may block sodium channels, a property unrelated to its ability to block 5-HT$_3$ receptors. Prolongation of the QTc interval is primarily due to QRS widening, and dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. The magnitude and frequency of the ECG changes associated with dolasetron use increase with dose (related to C$_{\text{max}}$ values of the active metabolite hydrodolasetron).

We hypothesize that the potential signal for ventricular arrhythmias and cardiac arrest detected with dolasetron, but not ondansetron or granisetron, may be due to the different effects of the 5-HT$_3$-receptor antagonists in blocking cardiac sodium channels at the plasma concentrations arising from the therapeutic doses required to treat nausea and vomiting. Although granisetron is more effective compared with dolasetron/hydrodolasetron and ondansetron in blocking human cardiac sodium channels (hH1) (Figure), the plasma concentration calculated to result from an IV dose of 40 µg/kg may be insufficient to produce significant sodium channel blockade. We calculated plasma concentrations of ~184 nmol/L after administration of granisetron 40 µg/kg IV (calculated from prescribing information [PI], using molecular weight [MW] 348.9 and C$_{\text{max}}$ 64.3 ng/mL after administration of a 40-µg/kg IV dose). Thus, it may be even less likely that the dose (10 µg/kg) of granisetron approved by the FDA for the prevention of chemotherapy-induced nausea and vomiting will produce such a blockade. Similarly, plasma concentrations produced following the administration of a 32-mg IV dose of ondansetron (~722 nmol/L; calculated from PI using MW 365.9 and C$_{\text{max}}$ 264 ng/mL) also seem insufficient to produce significant blockade of sodium channels (based on the inhibition vs concentration curve for ondansetron; Figure). This is in contrast with dolasetron, in which plasma concentrations following the administration of a 100-mg IV dose (~730 nmol/L; calculated from PI using MW 438.5 and C$_{\text{max}}$ 320 ng/mL) cause more sodium channel blockade compared with either ondansetron 32 mg IV or granisetron 40 µg/kg IV (based on the inhibition vs concentration curve for hydrodolasetron; Figure).

The C$_{\text{max}}$ values used to calculate plasma concentrations were from healthy volunteers, as documented in each drug's PI, rather than patients with cancer.
Figure. Inhibitory effects of granisetron, ondansetron, and hydrodolasetron (the active metabolite of dolasetron) on cardiac sodium channels. Calculated IC\textsubscript{50} values were 2.6 \mu M for granisetron, 88.5 \mu M for ondansetron, and 8.5 \mu M for dolasetron (hydrodolasetron). Cardiac sodium channel blockade by the C\textsubscript{max} values arising from specific doses of granisetron, ondansetron, and dolasetron have been predicted by superimposing their C\textsubscript{max} values onto a graph and reading from the respective curves. These calculations were based on the following: granisetron 40 \mu g/kg IV, molecular weight (MW) 348.9, C\textsubscript{max} 64.3 \text{ ng/mL}\textsuperscript{29}; ondansetron 32 mg IV, MW 365.9, C\textsubscript{max} 264 \text{ ng/mL}\textsuperscript{28}; dolasetron 100 mg IV, MW 438.5, C\textsubscript{max} 320 \text{ ng/mL}\textsuperscript{27} \textsl{I}\textsubscript{Na} = sodium channel current. Adapted with permission.\textsuperscript{3}

C\textsubscript{max} data are available from patients with cancer in the PI for dolasetron and granisetron but not for ondansetron 32 mg. The calculated plasma concentration following the administration of a 1.8-mg/kg dose of dolasetron is ~1152 nmol/L (calculated from PI\textsuperscript{27} using MW 438.5 and C\textsubscript{max} 505 ng/mL), which may produce even greater sodium channel blockade than suggested from the data obtained from healthy volunteers (Figure). In contrast, the plasma concentration following the administration of granisetron 40 \mu g/kg IV in patients with cancer (182 nmol/L) is similar to that predicted in healthy volunteers (calculated from PI\textsuperscript{29} using MW 348.9 and C\textsubscript{max} 63.8 ng/mL after administration of a 40-\mu g/kg IV dose). It should be noted, however, that we are comparing C\textsubscript{max} values in healthy vol-
unteers and patients with cancer with those from in vitro inhibition experiments conducted in noncancer cell lines (on which estimations of sodium channel blockade are based). 3

**Human ether-a-go-go–related** gene (HERG) potassium channels are thought to be important for the repolarizing current in the human heart and are a determinant of the QT interval. 3 Drugs that block potassium channels may produce QT prolongation, whereas drugs that block sodium hH1 channels may lead to widening of the QRS interval (which can prolong the QTc interval), 3,27 and in both cases ventricular arrhythmias may result. 3 The effects of dolasetron, ondansetron, and granisetron on the human cardiac potassium channels have also been investigated. 3 In those studies, the rank order of potency for these agents to block HERG potassium channels was ondansetron > granisetron > dolasetron > hydrodolasetron, and the authors suggest that the reported prolongation of cardiac repolarization observed with ondansetron 9,17 may be due to its ability to block the cardiac potassium channel. Although the reported changes in ECG intervals observed after administration of ondansetron 32 mg IV were transient and asymptomatic, 9,17 Kuryshev et al 3 predicted that high heart rates or other situations that favor activated states of the potassium channel may enhance the inhibition of the HERG channel by ondansetron. 3

A review by Navari and Koeller 35 suggested that ECG interval changes are a class effect of the 5-HT3-receptor antagonists and that they possess only a small theoretical risk for meaningful cardiovascular events. However, it is argued that current evidence concerning ECG changes with 5-HT3-receptor antagonists suggests that, in clinical practice, QTc interval prolongation should be considered less of a “class effect” and more a “dose effect.” 36 As discussed by Navari and Koeller, 35 ECG changes caused by dolasetron use have been observed in healthy volunteers and in controlled trials, and their magnitude and frequency increased with dose. 27 In studies in healthy volunteers, dolasetron has resulted in significant dose-related, dose-dependent increases in QTc interval. 5,16 Similarly, dose-related increases in QTc interval have been observed 1 to 2 hours following dolasetron administration in patients receiving chemotherapy. 11,14

Furthermore, the ECG changes associated with dolasetron use have been observed in clinical studies despite the fact that many patients who may be at increased risk for QTc interval prolongation (eg, patients with cardiac comorbidities or irregularities, 4,7,10–14 or those receiving certain antiarrhythmic medications 4,7,10,11) were excluded. Moreover, given that patients with cancer are typically over the age of 65 years, 30 have a high incidence of cardiovascular comorbidities (~60% of patients aged >70 years 35), and are likely to be consuming multiple medications, 31 there may be the potential for additive QT effects in patients with cancer already at risk for cardiovascular complications. 38,39

When choosing a 5-HT3-receptor antagonist in a patient who has or may develop prolongation of cardiac conduction intervals, particularly QTc (including patients with hypokalemia, hypomagnesia, or congenital QT syndrome, or those receiving diuretics with the potential for inducing electrolyte abnormal-
ties, antiarrhythmic drugs or other drugs that might lead to QT prolongation, or cumulative high-dose anthracycline therapy), it would seem prudent to use an effective 5-HT₃-receptor antagonist that has no warning or precautionary statements in its FDA labeling concerning prolongation of cardiac conduction intervals (including QTc prolongation).

**CONCLUSIONS**

This analysis of the FDA SRS/AERS database suggests a potential signal for ventricular arrhythmias and cardiac arrest with dolasetron, but not with ondansetron or granisetron. Although there are limitations to the PRR analysis, the presence of a potential signal for ventricular arrhythmias and cardiac arrest with dolasetron suggests that further research into the potential signal may be necessary.

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**REFERENCES**


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