Pharmacokinetics and Repolarization Effects of Intravenous and Transdermal Granisetron

Running title: Transdermal Granisetron Pharmacokinetics and Cardiac Effects

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Figures and tables: 8 (6 tables, 2 figures)**Statement of translational relevance:** The need for greater clarity about the effects of 5-HT_3 receptor antagonists on cardiac repolarization is apparent in product label changes for this therapeutic class. Our study assessed repolarization effects of intravenous (IV) and transdermal (GTDS) granisetron, a 5-HT_3 receptor antagonist antiemetic, placebo, and moxifloxacin (active control) in healthy subjects. The primary end point was difference in change from baseline in mean Fridericia-corrected QT interval (QTcF) between GTDS and placebo (ddQTcF). The results showed that GTDS was not associated with any statistically or clinically significant effects on QTcF or any other measured ECG variables. Our study provides useful clarification on the lack of effect of granisetron on cardiac repolarization at the plasma concentrations delivered by

GTDS, and will allow practitioners to make more informed decisions regarding the use of this agent for prophylactic antiemetic therapy.

ABSTRACT

Purpose: The need for greater clarity regarding the effects of 5-HT_3 receptor antagonists on cardiac repolarization is apparent in the changing product labeling across this therapeutic class. This study was assessed repolarization effects of granisetron, a 5-HT_3 receptor antagonist antiemetic, administered intravenously and by a granisetron transdermal system (GTDS).

Methods: In a parallel 4-arm study, healthy subjects were randomized to receive intravenous (IV) granisetron, GTDS, placebo, or oral moxifloxacin (active control). The primary end point was difference in change from baseline in mean Fridericia-corrected QT interval (QTcF) between GTDS and placebo (ddQTcF) on days 3 and 5.

Results: A total of 240 subjects were enrolled, 60 in each group. Adequate sensitivity for detection of QTc change was demonstrated by a 5.75 ms lower bound of the 90% confidence interval (CI) for moxifloxacin vs placebo at 2 hours post-dose on day 3. Day 3 ddQTcF values varied between 0.2 and 1.9 ms for GTDS (maximum upper bound of 90% CI, 6.88 ms), between –1.2 and 1.6 ms for IV granisetron (maximum upper bound of 90% CI, 5.86 ms), and between –3.4 and 4.7 ms for moxifloxacin (maximum upper bound of 90% CI, 13.45 ms). Day 5 findings were similar. Pharmacokinetic–ddQTcF modeling showed a minimally positive slope of 0.157 ms/(ng/mL), but a very low correlation (r = 0.090).

Conclusion: GTDS was not associated with statistically or clinically significant effects on QTcF or other ECG variables. This study provides useful clarification on the effect of granisetron delivered by GTDS on cardiac repolarization.

INTRODUCTION

Granisetron and other 5-HT_3 receptor antagonists are used extensively to prevent and suppress chemotherapy-induced nausea and vomiting (CINV)[1,2] and the nausea and vomiting that occurs during the postoperative period. However, experience has shown an association between these agents and cardiac repolarization. Although recognition of the potential for QT prolongation by non-cardiovascular therapies has resulted in intense regulatory interest in the identification and characterization of repolarization effects of new and approved drugs,[3] a study dedicated to the assessment of repolarization effects of the 5-HT_3 receptor antagonists has not yet been reported in the medical literature.

In a review of reports published between 1963 and 2002, Navari and Koeller[4] concluded that intravenous (IV) 5-HT_3 receptor antagonists do not pose a significant cardiovascular risk but, as pointed out by Keefe,[5] available data are inadequate to classify the risk as negligible, especially in patients with pre-existing cardiovascular disease and those receiving cardiotoxic chemotherapeutic agents. The need for greater clarity regarding QT prolongation in patients receiving 5-HT_3 receptor antagonists is apparent in the changing product labeling across this therapeutic class. Over the last 3 years, there have been changes in the labeling for several 5-HT_3 receptor antagonists relating to cardiac repolarization effects. The dolasetron (Anzemet®) prescribing information states that this medication can prolong the QT interval in a dose-dependent manner and, more recently, the IV formulation was contraindicated for antiemesis in CINV.[6,7] Prescribing information for both the oral[8] and intravenous (IV)[9] formulations of ondansetron (Zofran®) state that transient QT prolongation was identified during post-approval use rarely but predominantly

with IV administration. A warning was recently added to the label to avoid the use of ondansetron in patients with congenital long QT syndrome and to recommend electrocardiographic (ECG) monitoring in certain patient groups.[8,9] Oral and injection granisetron (Kytril®) prescribing information was updated recently to state that QT prolongation has been reported with this medication but indicates that an adequate assessment has not been done.[10,11] Palonosetron (Aloxi®) prescribing information reports QT prolongation as an adverse reaction, with an incidence ≥2% among postoperative surgical patients and <1% among patients with CINV, and reports that a double-blind randomized, parallel, placebo- and positive (moxifloxacin)-controlled trial in healthy adults demonstrated no significant effect on duration of the corrected QT interval (QTc).[12] Finally, the prescribing information for granisetron transdermal system (GTDS; Sancuso®) reports that a phase 3 study found QT prolongation in 2.7% of patients receiving oral granisetron but in only 1.1% in patients receiving GTDS.[13]

GTDS was approved by the US Food and Drug Administration (FDA) in September 2008 and is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days' duration.[13] GTDS is a drug-in-adhesive formulation of granisetron that is applied as a matrix patch to the upper outer arm for a minimum of 24 hours and a maximum of 48 hours before chemotherapy and removed a minimum of 24 hours after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen. The prolonged delivery of granisetron via GTDS was developed in an attempt to reduce pill burden and improve adherence to antiemetic treatment and to provide control of

nausea and vomiting with a lower maximum plasma concentration, thereby potentially reducing the possibility of any cardiotoxic effects. The 52-cm^2 patch contains 34.3 mg of granisetron delivered transdermally at a dosage of 3.1 mg/24 h for up to 7 days[13] and has been shown to achieve a similar granisetron exposure to that of a 2-mg oral dose of granisetron.[14] In the randomized, active control, double-blind, parallel group, phase 3 trial of GTDS in patients receiving multiday moderately or highly emetogenic chemotherapy, GTDS demonstrated noninferiority to oral granisetron in the control of CINV.[15]

The study presented here was designed in response to a request by FDA for a postmarketing assessment of the effect of the GTDS on QTc and was reviewed and approved by the agency's QT Interdisciplinary Review Team.[16] The objective was to provide a detailed assessment of the repolarization effect of GTDS and to compare it with that of IV granisetron.

MATERIALS AND METHODS

Study Design and Treatment

This was a phase I, single-site, single-blind (except for the open-label use of moxifloxacin), randomized, placebo- and positive-controlled, 4-arm parallel study to evaluate the effect of doses of GTDS and IV granisetron on the QT interval in healthy male and female subjects. Blinding was achieved by use of a placebo transdermal patch that matched the GTDS but contained adhesive without granisetron, and IV saline that matched the granisetron infusion system.

Subjects were admitted to the clinic 2 days before the first dose (day –2) and received study medication on day 1 (patch applied) and day 3 (IV treatment administered or oral moxifloxacin given). On day 1, GTDS (Sancuso®; ProStrakan, Bedminster, NJ) or its placebo was applied to the skin of the upper arm of all subjects. On day 3, IV granisetron 0.1 mg/10 kg body weight (generic granisetron hydrochloride [1 mg/mL solution] single IV injection) or its placebo was administered over 30 seconds. Moxifloxacin 400 mg tablets (Avelox®, Bayer HealthCare, Wayne, NJ) were administered orally at day 3 and the placebo patch was removed after 3 days. *Group 1* received the GTDS patch on day 1 for 5 days and IV placebo on day 3, *group 2* received the placebo patch on day 1 for 5 days and IV granisetron on day 3, *group 3* received placebo patch on day 1 for 5 days and IV placebo on day 3, and *group 4* received the placebo patch on day 1 for 3 days and moxifloxacin on day 3. Treatment with GTDS comprised application of 1 patch for 5 days, which was the recommended therapeutic dose in the United States and allowed blood sampling for pharmacokinetics on day 3 that covered the predicted maximal observed analyte concentration (C_{max}) of granisetron administered by this method. The dose of IV granisetron, 10 μg/kg, was the approved US dose and was the dose requested by the FDA.

ECGs were taken daily in all 4 groups from day –1 to day 6 using a continuous 12-lead digital recorder, thereby covering the predicted period for granisetron C_{max}. Pharmacokinetic blood samples were obtained in all 4 groups daily from day 1 to day 6 in all but the moxifloxacin group, which was discharged from the clinic on the morning of day 4.

Subjects

Eligible subjects were in good health as determined by a physician, with a weight of ≥50 kg (110 lb) and a body mass index of 18–32 kg/m^2, and were judged capable of understanding and complying with the protocol. Major exclusion criteria were history of drug abuse, known hypersensitivity to the study drugs or related compounds, abnormal blood pressure or heart rate, significant findings on ECG including a Fridericia-corrected QTc interval (QTcF) of >430 ms in men and >450 ms in women, history of long QT syndrome, known presence or symptoms of cardiac disease, and electrolyte disturbances or a first-degree relative with an unexplained sudden death at <40 years of age.

All subjects signed the informed consent form. The study and its consent form were approved by the Chesapeake Research Review, Inc., IRB, Columbia, Maryland, and the study was conducted according to the protocol, the 21 Code of Federal Regulations, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation Guideline for Good Clinical Practice.

Electrocardiographic Measurements and Interpretation

Electrocardiograms were obtained digitally using a continuous 12-lead digital recorder, on day –1 (baseline), and on days 1, 2, 3, and 4 (all treatment groups), and on days 5 and 6 (treatment groups 1, 2, and 3) of the study. Electrocardiograms used in the analysis were selected by predetermined time points and were read centrally using a high-resolution manual on-screen caliper method with annotations. Three 12-lead ECGs were measured within 1 minute of each time point. A window of ±3 minutes around each time point was

used for the central reader to obtain the necessary ECGs. Time points for ECGs were 0 hour (pre-dose) for all groups on days 1, 2, and 4 and for groups 1, 2, and 3 on day 6; 0, 4, and 12 hours for groups 1, 2, and 3 on day 5; and 0 hour, immediately after the scheduled dose, and at 0.25, 0.5, 1, 2, 4, 8, 12 hours for all groups on days –1 and 3.

If the initial 30 ECG measurements from baseline (days –1 and 1) could not adequately construct an individual QT correction (QTcI), more baseline ECGs were retrospectively retrieved from the telemetry system to provide an accurate QTcI. However, only the original ECGs at baseline were used to establish baseline ECG interval values. A total of 75 ECGs (groups 1, 2, and 3) and 63 ECGs (group 4) per subject were collected for analysis.

As part of the ECG reading process, the cardiologist inserted or deleted diagnostic statements on all records. Diagnostic statements related to repolarization were analyzed in detail. The core ECG laboratory staff remained blinded to treatment, time, and study day identifier, and all ECGs from a particular subject were read by a single reader.

Statistical Methods

Primary End Point

QT corrected by the Fridericia formula[17] was the primary variable, and the primary end point was the difference between the post-dose, time-matched change from baseline in mean QTcF (dQTcF) of the GTDS group (group 1) and dQTcF of the placebo group (group 3), or ddQTcF, where $ddQTcF = dQTcF_{GTDS} - dQTcF_{placebo}$.

The null hypothesis for the primary end point was that the baseline-adjusted difference between the mean dQTcF of GTDS minus that of placebo (ddQTcF) was ≥10 ms versus the alternative that the ddQTcF was <10 ms for the post-treatment hours. The value of 10 ms (as the upper bound of the 95% 1-sided confidence interval [CI] for the largest time-matched mean effect of the drug on the QTc interval) represented the threshold level of regulatory concern regarding QTc prolongation.[3]

The simultaneous hypotheses for the post-treatment hours were tested with a mixed effects model for repeated measures with change from baseline (dQTcF) as the dependent variable and factors for treatment group, time point, and the interaction of treatment group by time point, with baseline as covariate. Two-sided 90% CIs for the ddQTcF were calculated from the model for each post-dose time point and were used to test the statistical hypothesis. If at least one of the upper bounds was ≥10 ms, this suggested a treatment effect on the QTcF. A conclusion of no clinically meaningful treatment effect on the QTcF would be reached if all upper bounds were <10 ms.

Sensitivity Analysis

An additional analysis was performed to assess assay sensitivity using the placebo (group 3) and moxifloxacin (group 4) groups. The hypotheses for this analysis are slightly different from the primary analysis, but the model and model statements are the same. This hypothesis involves testing only at 1, 2, and 4 hours post-treatment on day 3. Moxifloxacin was chosen as a positive control to test assay sensitivity because of its known QT-prolongation effects, so a difference between the two groups was expected. Therefore, if

the lower bound of the 2-sided 90% CI was >5 ms for any of the 3 time points, assay sensitivity would be confirmed. However, if all of the lower bounds were <5 ms, the null hypothesis would not be rejected and assay sensitivity would not be validated.

Secondary ECG End Points

Secondary end points included categorical QTcF values (>450, >480, and >500 ms) and changes (>30 and >60 ms), day 3 QTc measured with Bazett correction method (QTcB) parameters (including change from baseline [dQTcB] and baseline-adjusted difference between GTDS and placebo [ddQTcB]) using the same model as for the primary analysis, and the incidence of T-wave and ST-segment abnormalities associated with IV granisetron on day 3 and day 5.

Pharmacokinetic and Pharmacodynamic Methods

Individual profiles of granisetron plasma concentration vs actual time after dosing were generated for each subject. Blood samples for pharmacokinetic analysis were taken every day from day 1 to day 6. Pharmacokinetic parameters were estimated from the concentration data using the modeling package WinNonlin® for each subject (Pharsight Corporation, Mountain View, CA), including C_{max}; T_{max} (time to reach C_{max}); AUC_{0-z} (area under the analyte vs time concentration curve from time of administration up to the time of the last quantifiable concentration, calculated by the linear trapezoidal summation method); and $AUC_{0-infinity}$ (area under the analyte vs time concentration curve from time of administration up to infinity, calculated as $AUC_{infinity} = AUC_{last} + C_{last}/\lambda_z$). Standard

descriptive statistical summaries of subject characteristics and pharmacokinetic parameters for each treatment were prepared.

A secondary objective was to observe the relationship between changes in QTcF and granisetron plasma concentrations. Unadjusted ddQTcF values from the subset of the population receiving GTDS (group 1) and IV granisetron (group 2) that had at least one post-dose plasma concentration were used for this analysis. The mixed-effects model included plasma concentration as a dependent variable and subject as a random effect. From this model, an estimate of the population ddQTcF was obtained over the range of plasma concentration values. The ddQTcF and 90% CIs were estimated at the minimum, median, and maximum plasma concentrations. The slope and correlation coefficient of the regression were calculated.

Safety

Vital signs and the frequency and severity of adverse events (AEs) and were measured daily from screening to day 6. Any AEs occurring after first application of study medication were classified as treatment-emergent AEs and were determined by questioning the subjects, investigator observation of subjects, and spontaneous reporting by subjects. The relationship of any AE to study medication (not related, possible, probable, or definite) was determined by the investigator. Serious AEs were also recorded. Physical examination was conducted at screening, admission, and at follow-up, standard clinical laboratory tests were conducted by the local laboratory at screening and at post-study evaluation.

Sample Size Calculation

The sample size of approximately 240 healthy male and female subjects was calculated by the summary means method of Zhang and Machado,[18] and the study design was based on the ICH e-14 Guidance as well as direct recommendations from the US Food and Drug Administration.[3] Assuming a 1-sided 0.05 significance level, an average standard deviation of QTcF of ≤11 ms (observed from previous unpublished studies by the sponsor), up to 10 post-treatment assessment time points, and 3 replicate ECGs at each ECG assessment time point, a total of 60 subjects in each of the 4 treatments groups was deemed sufficient to achieve a ≥90% power to exclude a prolongation of ≥10 ms for all time-matched ddQTcF, also assuming a mean baseline-adjusted prolongation of 3 ms with placebo. Use of the union-intersection test permitted testing at all post-dose time points.

RESULTS

Subject Characteristics

The study was conducted between May and August, 2009. Sixty subjects were allocated to each of the 4 treatment groups. The study population was predominantly white (57.5%), had a mean age of 29.7 years (range 18–49 years), and included a similar proportion of men (49.6%) and women (50.4%) [**Table 1**]. There were no marked differences between the treatment groups with respect to any demographic or baseline characteristics. Of the 240 enrollees, 239 completed the study. A 27-year old woman randomized to IV granisetron withdrew from the study for personal reasons on day 3 before receiving IV granisetron.

Electrocardiography

Repolarization

Primary end point results for GTDS and IV granisetron are displayed in **Table 2**. GTDS was associated with minimal changes in QTcF. The ddQTcF was consistently positive, but the maximum increase was only 1.9 ms, seen at 4 hours, and no change in ddQTcF was statistically significant. The treatment effect for the overall model was not significant (*P*=.7033). For IV granisetron, ddQTcF was generally negative, except at 0 hours, when it reached its maximum change of 1.6 ms. No change was statistically significant. Day 3 ddQTcF values for moxifloxacin varied between –3.4 and 4.7 ms (maximum upper bound of 90% CI, 2.56 ms), and no change was statistically significant.

Categorization of QTcF values before and during treatment and categorization of change in QTcF values during treatment showed no meaningful differences or patterns of change between the four groups (data not shown). A comparison of time-matched change from baseline to day 5 in mean QTcB between GTDS and placebo (ddQTcB) at 0, 4, 12, and 24 hours post-dose showed consistently negative ddQTcB values, ranging from –1.5 ms at 12 hours to –4.8 ms at 24 hours (maximum upper bound of 90% CI 13.45 ms).

The number of subjects in each group with >450 ms, >480 ms, and <500 ms QTcF values during days 2 to 5 and the number of subjects in each group with >30 ms and >60 ms changes from baseline in QTcF (dQTcF) and are shown in **Table 3**. No subject in any group had QTcF >500 ms, and no subject in any group had dQTcF >60 ms.

No abnormal U waves were detected on any ECG recordings in this study. There was no difference between the groups in the incidence or change in abnormal morphology diagnoses involving the ST segment or T wave. A random sampling of ECGs with abnormal T-wave, ST–T abnormalities, and long QT interval diagnoses was examined by a cardiologist; the sampling included at least 5 ECGs obtained for each group at a specific time point on days –1, 3, and 5, during which a sufficient number of abnormal ECGs were recorded. This review showed consistently mild abnormalities, including mild T-wave flattening, inversion of the T-wave in the inferior leads and minor terminal negativity of the T-wave in the precordial leads (both considered by most experts to be normal), mild ST flattening or elevation (<1 mm), and minimal lengthening of QTc (QTcF was >480 ms on only 9 ECGs of 4 subjects during treatment). None of the changes suggested a significant disturbance of repolarization. Incidences of these abnormalities and their fluctuation over time were nearly identical for the 4 treatment groups and showed no consistent pattern of change from baseline (day –1).

Sensitivity Assay

The sensitivity analysis (**Figure 1**), which was carried out using data from the placebo and moxifloxacin groups at 1, 2, and 4 hours after treatment, indicated adequate sensitivity of study design and methods for detection of a small change in QTcF. The maximum moxifloxacin-related ddQTcF was 9.1 ms, with a 90% CI lower bound of 5.75 ms.

Other ECG Findings

Variations in heart rate, PR interval, and QRS duration were within limits expected for normal volunteers under the experimental conditions of this study. There were no clinically significant differences between the groups and no trends of change consistent with a drug effect.

Pharmacokinetics

The pharmacokinetic observations for GTDS, IV granisetron, and oral moxifloxacin are shown in **Table 4**. For GTDS, the mean maximum plasma concentration was reached at 56 hours after patch application, and mean plasma concentration remained relatively stable until 96 hours after application, at which time mean concentrations began to decline slowly (not shown). There was high intersubject variability observed by the shape of the curves and the concentrations measured at each sampling time point. The highest individual C_{max} value was 18.7 ng/mL, seen at 48 hours after patch application (not shown). Mean granisetron plasma concentrations across the entire period, AUC_{0-120h}, and median T_{max} were higher in women than men, although there was considerable overlap between the ranges of individual values. For IV granisetron, the mean maximum plasma concentration was reached at 0.6 hours post-dose and quantifiable plasma concentrations decreased below the lower limits of quantification by 48 hours in many subjects. As in the GTDS group, the IV granisetron group had higher mean granisetron plasma concentrations in women than in men; however, the difference was somewhat smaller in the IV granisetron group. The highest individual observed C_{max} value was 26.1 ng/mL (**Table 5**). Mean $AUC_{0-infinity}$ and median T_{max} were higher in women than in men, and C_{max} was slightly lower in women, which is primarily the result of one relatively high C_{max} value in one male subject. In

the oral moxifloxacin group, the mean maximum plasma concentration was reached 4 hours post-dose, after which plasma concentrations declined.

Pharmacodynamics

Results of analysis of the relationship between plasma concentration and change in QTcF are shown in **Figure 2** and **Table 5**. There is a very weak (r = 0.09), positive correlation consistent with a small effect of granisetron on QTcF. At the maximum granisetron concentration observed in this study, the model predicts an increase in QTcF of <5 ms.

Safety

All 240 subjects (60 in each group) were evaluable for safety. The mean duration of patch application was 120 hours for groups 1 and 3, 118.9 hours for group 2 (1 patient withdrew at day 3), and 72 hours for group 4. The mean dose of IV granisetron administered was 0.733 mL at a 1 mg/mL concentration, equivalent to 733 µg granisetron (administered at 10 µg/kg). The mean amount of granisetron delivered through the GTDS during the 5-day treatment period was calculated to be 17.65 mg, resulting in a flux of 3.53 mg/24 h.

The incidence of subjects reporting at least 1 treatment-emergent AE was 53% (n=32) for group 1 (GTDS), 27% (n=16) for group 2 (IV granisetron), 45% (n=27) for group 3 (placebo), and 30% (n=18) for group 4 (moxifloxacin). The majority of AEs experienced during the study were considered mild in severity for all treatment groups. Adverse events considered to be at most moderate in severity occurred in 6 subjects (10.0%) receiving GTDS (group 1), 1 subject (2%) receiving IV granisetron (group 2), 4 subjects (7%)

receiving placebo (group 3), and 1 subject (2%) receiving moxifloxacin (group 4). One subject treated with GTDS experienced a severe AE of headache on day 3 that was considered probably related to treatment and that resolved on the same day.

The majority of AEs were considered by the investigator to be related to treatment. **Table 6** summarizes treatment-related AEs reported in at least 1 patient. The most frequently reported AE in each group was application site erythema related to patch application (group 1: 22%; group 2: 10%; group 3: 12%; group 4: 13%). The incidence of treatment-related headache was higher with GTDS (group 1; 7%) and IV granisetron (group 2; 10%) than with placebo (group 3; 3%) or moxifloxacin (group 4; 3%). The incidence of treatment-related constipation was 17% with GTDS (group 1), which was higher than the 2% each reported with IV granisetron (group 2) and placebo (group 3) and 0% with moxifloxacin (group 4).

There were no deaths or other serious AEs reported during the study, and no AEs that led to study drug discontinuation.

DISCUSSION

This study demonstrates minimal effect of granisetron, when used in accordance with package labeling, on cardiac repolarization. Though change in QTcF was not statistically significant during treatment with IV granisetron or GTDS at any time point, the pharmacokinetic/pharmacodynamic relationship, drawn from data from both groups, is consistent with a small QT-prolonging effect of granisetron, though the weak correlation

between concentration and effect reduce the reliability of this conclusion. ddQTcF was slightly negative at 6 of 9 time points on day 3 during treatment with IV granisetron and positive at all 9 time points during treatment with GTDS. This may be a result of a rapid fall in C_{max} for IV granisetron, despite it being slightly higher than for GTDS, while the C_{max} was sustained for GTDS. Exposure to granisetron in the GTDS group through 5 days did not alter the effects observed on day 3 of exposure, and the absence of an effect of granisetron on heart rate, PR interval, and QRS duration persisted through day 5.

The need for greater clarity regarding the effects of 5-HT_3 receptor antagonists on cardiac repolarization is apparent in the changing product labeling across this therapeutic class. Labeling within the class of 5-HT3 receptor antagonist antiemetic drugs is inconsistent with regard to QT prolongation, which is classified as a precaution for oral and IV formulations of granisetron[10,11] and a warning for oral ondansetron but not IV ondansetron,[8,9] as well as the removal of a warning from the package insert for IV palonosetron.[12] Furthermore, Roche issued a drug warning separate from the label indicating that QTc prolongation has been reported for Kytril (IV and oral granisetron), and that this medication should be used with appropriate caution.[13] Recently, IV dolasetron (Anzemet®) was contraindicated for CINV because of QT prolongation[6] and, while the same warning and precaution regarding QT prolongation is listed in the labeling of the oral and IV formulations, the FDA has stated that the oral formulation may still be used to treat CINV.[9,19]

There are conflicting reports in the literature on the effects of granisetron on ECG findings.[20,21] This lack of clarity is in part due to the fact that an appropriately designed

study had not previously been performed to accurately determine the repolarization effects of granisetron or any other drug in its class. This study showed a small effect of granisetron.

The pharmacokinetics of GTDS compared with those of IV granisetron were as expected: C_{max} was lower for GTDS than for IV granisetron (3.63 vs 4.95 ng/mL, respectively), T_{max} was higher for GTDS (56.08 vs 0.57 h), and the AUC_{0-120h} for GTDS was higher than the $AUC_{0-infinity}$ for IV granisetron (238.5 vs 36.87 ng·h/mL). Intersubject variability of pharmacokinetics was high for both GTDS and IV granisetron, although lower for GTDS, and exposure was higher in women than in men for both GTDS and IV granisetron, although there was considerable overlap in the ranges of individual values.

Our findings suggest that granisetron delivered by the IV or transdermal route is generally safe in healthy volunteers with respect to its effect on cardiac repolarization. However, our modeling suggests that very high plasma concentrations of granisetron could be associated with clinically significant increases in QTc, though this possibility is only weakly supported by pharmacodynamics analyses. Since there is large interindividual variation in plasma concentrations of granisetron achieved by any route of administration,[10,11,13,14,22-24] treatment with doses higher than recommended should be administered cautiously. Use of granisetron in patients with disorders that reduce repolarization reserve[25] or in those who are receiving concomitant drugs that prolong the QT interval requires careful monitoring.

Interestingly, data from the randomized, double-blind, phase 3 trial of GTDS in patients who were receiving multiday moderately or highly emetogenic chemotherapy showed no clinically significant changes in ECG morphology and no cases of QTc prolongation.[15] Furthermore, in a recent post hoc analysis of data from this study, no clinically relevant changes were noted in repolarization intervals, ECG morphology, or heart rate from baseline in either the GTDS or the oral granisetron groups.[26]

Results of the current study demonstrate that GTDS achieved more prolonged therapeutic plasma concentrations of drug than IV granisetron. The prolonged exposure did not result in significant or progressive QT prolongation. This study provides useful clarification on the effect of granisetron delivered intravenously and by GTDS on cardiac repolarization.

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Table 1. Subject characteristics

Parameter/ Statistics	GTDS Group 1 n=60	IV Granisetron Group 2 n=60	Placebo Group 3 n=60	Moxifloxacin Group 4 n=60	Total N=240
Age, y					
Mean (SD)	29.9 (9.01)	30.3 (8.51)	29.7 (8.63)	29.0 (9.32)	29.7 (8.83)
Min, Max	18, 46	18, 48	18, 48	18, 49	18, 49
Gender, n (%)					
Male	30 (50.0)	31 (51.7)	29 (48.3)	29 (48.3)	119 (49.6)
Female	30 (50.0)	29 (48.3)	31 (51.7)	31 (51.7)	121 (50.4)
Race, n (%)					
White	33 (55.0)	36 (60.0)	41 (68.3)	28 (46.7)	138 (57.5)
African American	19 (31.7)	21 (35.0)	15 (25.0)	23 (38.3)	78 (32.5)
Other	8 (13.3)	3 (5.0)	4 (6.7)	9 (15.0)	24 (10.0)
Weight, kg					
Mean (SD)	73.37 (11.508)	73.42 (12.104)	73.14 (9.982)	72.55 (10.797)	73.12 (11.061)
Min, Max	50.1, 97.6	50.1, 100.5	51.4, 101.0	50.3, 96.8	50.1, 101.0

GTDS, granisetron transdermal delivery system; IV, intravenous; Min, Max, minimum, maximum; SD, standard deviation.

Table 2. Difference between the day 3 post-dose, time-matched change from baseline in mean QTcF (dQTcF) GTDS (group 1) and IV granisetron (group 2) compared with dQTcF of the placebo group (ddQTcF, where ddQTcF = $dQTcF_{GTDS} - dQTcF_{placebo}$)

Post-dose Time point	Difference in LS means	90% CI	*P* value	Difference in LS means	90% CI	*P* value
	GTDS			IV Granisetron		
0 h	1.1	(–3.59, 5.73)	0.7031	1.6	(–2.74, 5.86)	0.5486
0.25 h	0.2	(–4.36, 4.69)	0.9515	–1.1	(–5.36, 3.25)	0.6847
0.5 h	1.7	(–3.10, 6.55)	0.5540	–0.7	(–5.02, 3.58)	0.7828
1 h	1.0	(–3.55, 5.46)	0.7264	–1.2	(–5.54, 3.06)	0.6339
2 h	1.7	(–3.09, 6.45)	0.5610	0.5	(–3.85, 4.76)	0.8604
4 h	1.9	(–3.05, 6.88)	0.5236	–1.0	(–5.33, 3.29)	0.6947
8 h	0.3	(–4.08, 4.71)	0.9050	–0.9	(–5.21, 3.39)	0.7258
12 h	0.4	(–4.21, 4.99)	0.8877	–0.5	(–4.85, 3.76)	0.8344
24 h	0.5	(–3.67, 4.61)	0.8502	0.0	(–4.30, 4.31)	0.9975

Post-dose Time point	Difference in LS means	90% CI	*P* value	Difference in LS means	90% CI	*P* value
	GTDS			IV Granisetron		
Overall *P* values						
Treatment			0.7033			0.8687
Time			<0.0001			<0.0001
Treatment × Time			0.9705			0.8216

CI, confidence interval; GTDS, granisetron transdermal delivery system; IV, intravenous; LS, least squares.

Table 3. Subjects with specific QTcF values and specific changes from baseline in mean QTcF (dQTcF) for each treatment group

Measurement	Number of patients (%)			
	GTDS Group 1 n=60	IV Granisetron Group 2 n=60	Placebo Group 3 n=60	Moxifloxacin Group 4 n=60
QTcF, n (%)				
>450, ≤480 ms	1 (2)	3 (5)	6 (10)	3 (5)
>480, ≤500 ms	0 (0)	0 (0)	1 (2)	0(0)
>500 ms	0 (0)	0 (0)	0 (0)	0 (0)
dQTcF, n (%)				
>30, ≤60 ms	1 (2)	3 (5)	2 (3)	1 (2)
>60 ms	0 (0)	0 (0)	0 (0)	0 (0)

Table 4. Pharmacokinetics of GTDS, IV granisetron, and oral moxifloxacin during 5 days of study, overall and by gender

	All		Male		Female	
	Geometric Mean	%CV	Geometric mean	%CV	Geometric mean	%CV
GTDS						
N	59[a]		30		29	
C_{max}, ng/mL	3.629	83.30	2.908	79.14	4.563	78.15
T_{max}, h[b]	56.08 (23.82–119.83)		56.08 (23.83–119.83)		71.83 (23.82–119.83)	
AUC_{0-120h}, ng·h/mL	238.5	89.48	193.4	85.51	296.3	84.15
IV granisetron						
N	59[c]		31		28	
C_{max}, ng/mL	4.948	58.12	5.003	72.47	4.887	29.78
T_{max}, h[b]	0.57 (0.02–2.12)		0.33 (0.02–2.08)		0.58 (0.02–2.12)	
$AUC_{0-infinity}$, ng·h/mL	36.87	63.29	32.63	62.74	42.22	61.12
Oral moxifloxacin						
N	60		29		31	
C_{max}, ng/mL	2148	26.50	1826	21.83	2582	19.32
T_{max}, h[b]	4.07 (1.08, 4.15)		4.07 (1.08–4.08)		2.08 (2.07–4.15)	
AUC_{0-24h}, ng·h/mL	24880	21.27	21690	13.72	28280	17.62

[a]Pharmacokinetic parameters were not available for one subject.

[b]T_{max}: median (min, max).

[c]One subject withdrew prior to receiving granisetron injection.

AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; %CV, percent coefficient of variation; GTDS, granisetron transdermal system; IV, intravenous; T_{max}, time to C_{max}.

Table 5. Granisetron* pharmacokinetic-pharmacodynamic analysis

	Concentration, ng/mL	Predicted ddQTcF, ms	90% CI
Minimum	0.10	0.70	(–0.58, 1.98)
Medium	2.83	1.13	(–0.15, 2.41)
Maximum	26.10	4.79	(3.51, 6.07)
Correlation coefficient, r		0.090	
Linear slope		0.157 ms/(ng/mL)	

*Includes both GTDS and IV granisetron.

dQTcF, change in Fridericia-corrected QTc interval from baseline; ddQTcF, difference between the dQTcF in the moxifloxacin group and the dQTcF in the placebo groups; GTDS, granisetron transdermal system; IV, intravenous.

Table 6. Summary of treatment-related adverse events occurring in at least 1 subject

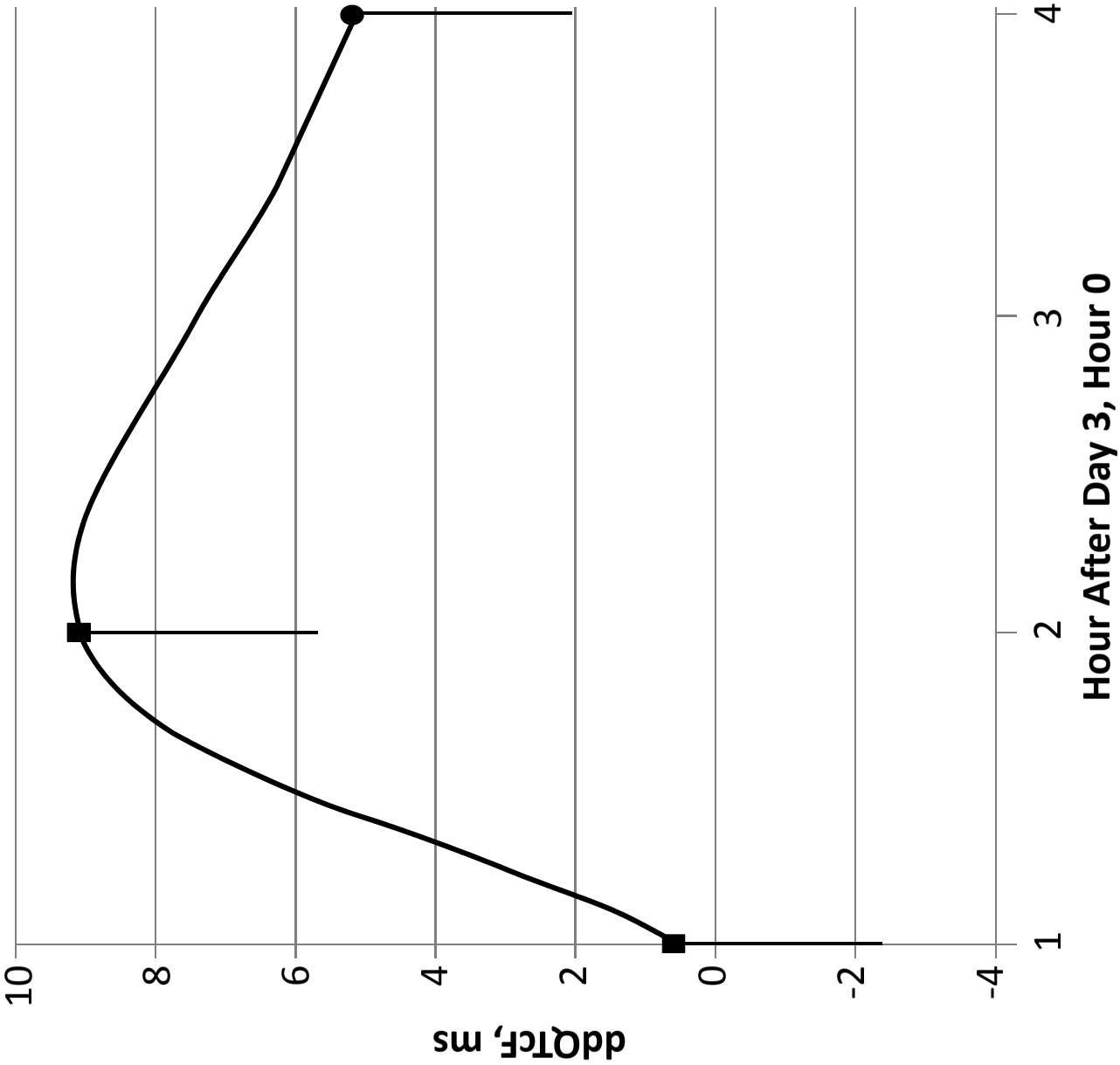
Adverse Event, n (%)	GTDS Group 1 n=60	IV Granisetron Group 2 n=60	Placebo Group 3 n=60	Moxifloxacin Group 4 n=60
Subjects with at least 1 treatment-related adverse event	29 (48)	13 (22)	21 (35)	14 (23)
Application site erythema	13 (22)	6 (10)	7 (12)	8 (13)
Constipation	10 (17)	1 (2)	1 (2)	0 (0)
Headache	4 (7)	6 (10)	2 (3)	2 (3)
Dizziness	2 (3)	1 (2)	2 (3)	0 (0)
Somnolence	1 (2)	3 (5)	3 (5)	1 (2)
Application site pruritus	1 (2)	0 (0)	3 (5)	1 (2)
Nausea	1 (2)	0 (0)	2 (3)	0 (0)
Flushing	1 (2)	0 (0)	1 (2)	0 (0)
Abdominal pain	1 (2)	0 (0)	0 (0)	0 (0)
Cardiac palpitations	1 (2)	0 (0)	0 (0)	0 (0)
Dry mouth	1 (2)	0 (0)	0 (0)	0 (0)
Irregular menstruation	1 (2)	0 (0)	0 (0)	0 (0)

Pain in extremity	1 (2)	0 (0)	0 (0)	0 (0)
Tremor	1 (2)	0 (0)	0 (0)	0 (0)

LEGENDS

Figure 1. ddQTcF, Moxifloxacin Sensitivity Assay. At hour 2 the least square mean difference between dQTcF for moxifloxacin was 9.1 ms and the 90% lower confidence bound was 5.75 ms. dQTcF, change in Fridericia-corrected QTc interval from baseline; ddQTcF, difference between the dQTcF in the moxifloxacin group and the dQTcF in the placebo groups.

Figure 2. QTcF–Plasma Concentration Relationship for Granisetron. Both GTDS and IV granisetron data were used to construct the model. The 90% confidence interval bounds are displayed. (Model parameters are shown in **Table 4**.) GTDS, granisetron transdermal delivery system; QTcF, Fridericia-corrected QTc interval; ddQTcF, difference between dQTcF in the moxifloxacin group and dQTcF in the placebo group.



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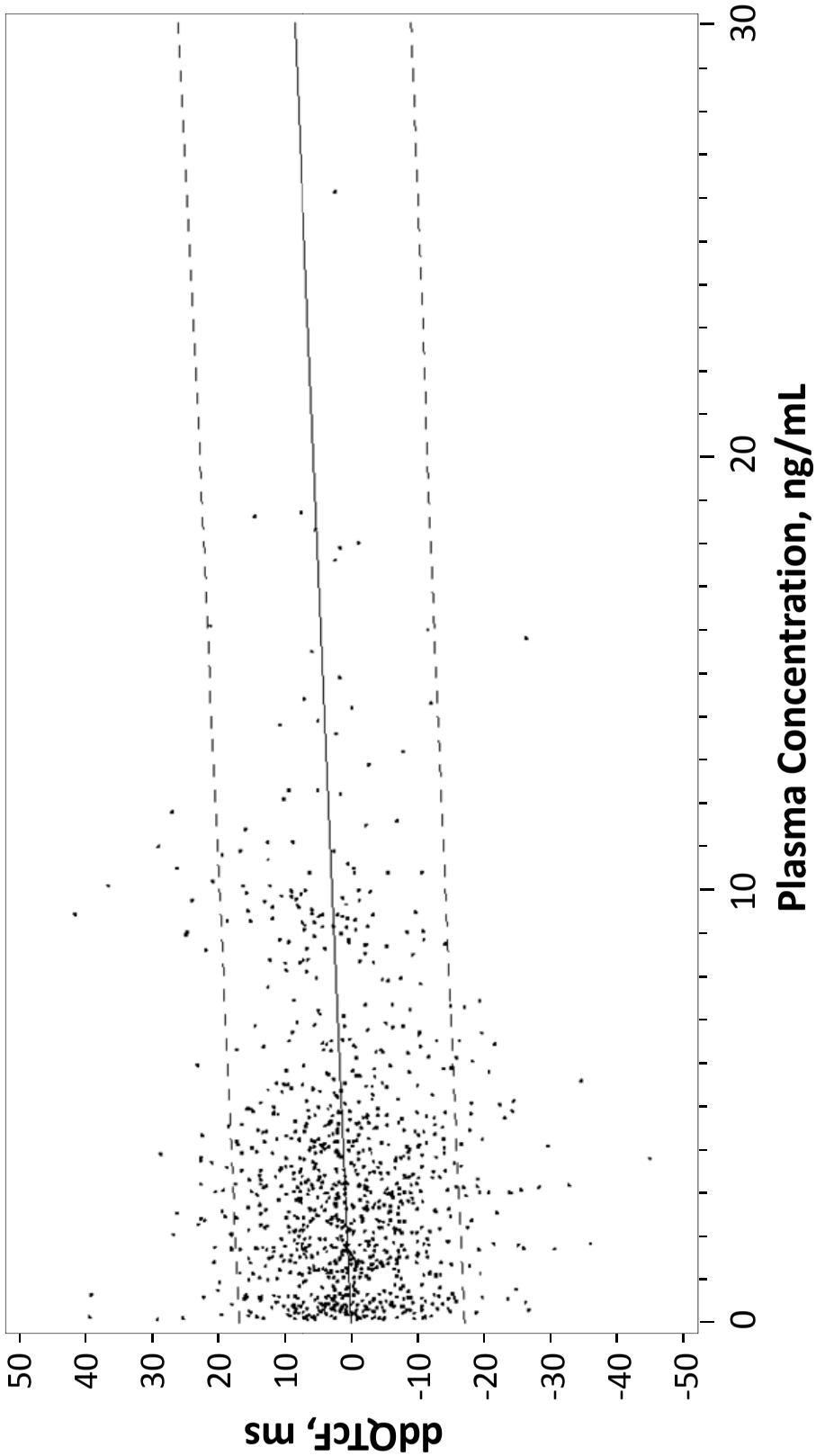

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