Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

Cancer Therapy: Clinical

Clinical Cancer Research

Pharmacokinetics and Repolarization Effects of Intravenous and Transdermal Granisetron

Jay W. Mason[1,2], Daniel S. Selness[2], Thomas E. Moon[2], Bridget O'Mahony[3], Peter Donachie[3], and Julian Howell[3]

Abstract

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

Experimental Design: In a parallel four-arm study, healthy subjects were randomized to receive intravenous granisetron, GTDS, placebo, or oral moxifloxacin (active control). The primary endpoint 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 shown by a 5.75 ms lower bound of the 90% confidence interval (CI) for moxifloxacin versus placebo at 2 hours postdose 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 i.v. 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 electrocardiographic variables. This study provides useful clarification on the effect of granisetron delivered by GTDS on cardiac repolarization. *Clin Cancer Res; 18(10); 2913–21. ©2012 AACR.*

Introduction

Granisetron and other 5-HT_3 receptor antagonists are used extensively to prevent and suppress chemotherapy-induced nausea and vomiting (CINV; refs. 1, 2) and the nausea and vomiting that occur 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 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 preexisting cardiovascular disease and those receiving cardiotoxic chemotherapeutic agents. The need for greater clarity about 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 i.v. formulation was contraindicated for antiemesis in CINV (6, 7). Prescribing information for both the oral (8) and intravenous (9) formulations of ondansetron (Zofran) state that transient QT prolongation was identified during postapproval use rarely but predominantly with i.v. 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

Authors' Affiliations: [1]University of Utah, Salt Lake City, Utah; [2]Spaulding Clinical Research, LLC, West Bend, Wisconsin; and [3]ProStrakan Pharmaceuticals Ltd, Galashiels, United Kingdom

Current address for B. O'Mahony: Quintiles Ltd, ALBA Business Park, Livingston, United Kingdom.

Corresponding Author: Jay W. Mason, Mason Cardiac Safety Consulting, 105 Londonderry Court, Reno, NV 89511. Phone: 775-849-9909; Fax: 775-849-9910; E-mail: jwm@jaywmason.com

doi: 10.1158/1078-0432.CCR-11-2785

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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 and transdermal (GTDS) granisetron, a 5-HT_3 receptor antagonist antiemetic; placebo; and moxifloxacin (active control) in healthy subjects. The primary endpoint 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 electrocardiographic 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 about the use of this agent for prophylactic antiemetic therapy.

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 $\geq$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 showed no significant effect on duration of the corrected QT interval (QTc; ref. 12). Finally, the prescribing information for granisetron transdermal system (GTDS; Sancuso) reports that a phase III study found QT prolongation in 2.7% of patients receiving oral granisetron but in only 1.1% of patients receiving GTDS (13).

GTDS was approved by the U.S. 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 III trial of GTDS in patients receiving multiday moderately or highly emetogenic chemotherapy, GTDS showed noninferiority to oral granisetron in the control of CINV (15).

The study presented here was designed in response to a request by the 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 i.v. 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 i.v. 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 i.v. 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 (i.v. treatment administered or oral moxifloxacin given). On day 1, GTDS (Sancuso; ProStrakan) or its placebo was applied to the skin of the upper arm of all subjects. On day 3, i.v. granisetron 0.1 mg/10 kg body weight [generic granisetron hydrochloride (1 mg/mL solution) single i.v. injection] or its placebo was administered over 30 seconds. Moxifloxacin 400 mg tablets (Avelox, Bayer HealthCare) 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 i.v. placebo on day 3, group 2 received the placebo patch on day 1 for 5 days and i.v. granisetron on day 3, group 3 received placebo patch on day 1 for 5 days and i.v. 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 i.v. granisetron, 10 μg/kg, was the approved U.S. dose and was the dose requested by the FDA.

ECGs were obtained daily in all 4 groups from day −1 to day 6, 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 $\geq$50 kg (110 lb) and a body mass

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

index of 18 to 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 more than 430 ms in men and more than 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 less than 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., Institutional Review Board, 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.

ECG measurements and interpretation

Electrocardiograms were obtained digitally using a continuous 12-lead digital recorder, on day −1 (baseline), 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 (predose) 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 endpoint. QT corrected by the Fridericia formula (17) was the primary variable, and the primary endpoint was the difference between the postdose, 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 $\text{ddQTcF} = \text{dQTcF}_{\text{GTDS}} - \text{dQTcF}_{\text{placebo}}$.

The null hypothesis for the primary endpoint 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 posttreatment hours. The value of 10 ms [as the upper bound of the 95% one-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 about QTc prolongation (3).

The simultaneous hypotheses for the posttreatment 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 postdose 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 less than 10 ms.

Sensitivity analysis. An additional analysis was conducted 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 posttreatment 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 2 groups was expected. Therefore, if the lower bound of the 2-sided 90% CI was longer than 5 ms for any of the 3 time points, assay sensitivity would be confirmed. However, if all of the lower bounds were shorter than 5 ms, the null hypothesis would not be rejected and assay sensitivity would not be validated.

Secondary ECG endpoints. Secondary endpoints 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 i.v. granisetron on days 3 and 5.

Pharmacokinetic and pharmacodynamic methods. Individual profiles of granisetron plasma concentration versus actual time after dosing were generated for each subject. Blood samples for pharmacokinetic analysis were taken everyday from days 1 to 6. Pharmacokinetic parameters were estimated from the concentration data using the modeling package WinNonlin for each subject (Pharsight Corporation), 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 $\text{AUC}_{0-\text{infinity}}$ (area under the analyte vs. time–concentration curve from time of

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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 i.v. granisetron (group 2) that had at least one postdose 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 and were measured daily from screening to day 6. Any adverse events occurring after first application of study medication were classified as treatment-emergent adverse events and were determined by questioning the subjects, investigator observation of subjects, and spontaneous reporting by subjects. The relationship of any adverse event to study medication (not related, possible, probable, or definite) was determined by the investigator. Serious adverse events 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 poststudy 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 FDA (3). Assuming a one-sided 0.05 significance level, an average SD of QTcF of $\leq$11 ms (observed from previous unpublished studies by the sponsor), up to 10 posttreatment 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 $\geq$90% power to exclude a prolongation of $\geq$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 postdose 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 i.v. granisetron withdrew from the study for personal reasons on day 3 before receiving i.v. granisetron.

Electrocardiography

Repolarization. Primary endpoint results for GTDS and i.v. 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 ($P = 0.7033$). For i.v. 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.

Table 1. Subject characteristics

Parameter/statistics	GTDS group 1 (N = 60)	Intravenous 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

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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

	GTDS		Intravenous granisetron	
Postdose time point, h	Difference in LS means (90% CI)	*P*	Difference in LS means (90% CI)	*P*
0	1.1 (−3.59, 5.73)	0.7031	1.6 (−2.74, 5.86)	0.5486
0.25	0.2 (−4.36, 4.69)	0.9515	−1.1 (−5.36, 3.25)	0.6847
0.5	1.7 (−3.10, 6.55)	0.5540	−0.7 (−5.02, 3.58)	0.7828
1	1.0 (−3.55, 5.46)	0.7264	−1.2 (−5.54, 3.06)	0.6339
2	1.7 (−3.09, 6.45)	0.5610	0.5 (−3.85, 4.76)	0.8604
4	1.9 (−3.05, 6.88)	0.5236	−1.0 (−5.33, 3.29)	0.6947
8	0.3 (−4.08, 4.71)	0.9050	−0.9 (−5.21, 3.39)	0.7258
12	0.4 (−4.21, 4.99)	0.8877	−0.5 (−4.85, 3.76)	0.8344
24	0.5 (−3.67, 4.61)	0.8502	0.0 (−4.30, 4.31)	0.9975
Overall *P*				
Treatment		0.7033		0.8687
Time		<0.0001		<0.0001
Treatment × time		0.9705		0.8216

Abbreviation: LS, least-squares.

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 4 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 postdose 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, >480, and >500 ms QTcF values during days 2 to 5 and the number of subjects in each group with >30 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 change >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

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

	Number of patients (%)			
Measurement	GTDS group 1 (N = 60)	Intravenous granisetron group 2 (N = 60)	Placebo group 3 (N = 60)	Moxifloxacin group 4 (N = 60)
QTcF				
>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 change				
>30, ≤60 ms	1 (2)	3 (5)	2 (3)	1 (2)
>60 ms	0 (0)	0 (0)	0 (0)	0 (0)

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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 (Fig. 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.

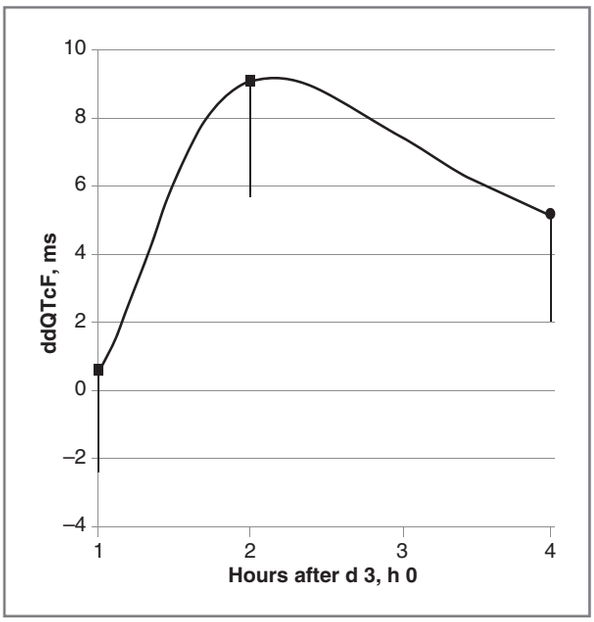

Figure 1. ddQTcF, moxifloxacin sensitivity assay. At hour 2, the least-square mean difference between dQTcF for moxifloxacin was 9.1 ms and the 90% lower confidence bound was 5.75 ms.

Pharmacokinetics

The pharmacokinetic observations for GTDS, i.v. 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

Table 4. Pharmacokinetics of GTDS, i.v. 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
Intravenous 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	2,148	26.50	1,826	21.83	2,582	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	24,880	21.27	21,690	13.72	28,280	17.62

Abbreviation: %CV, percent coefficient of variation.

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

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

[c]One subject withdrew before receiving granisetron injection.

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

Table 5. Granisetron pharmacokinetic–pharmacodynamic analysis

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

NOTE: Granisetron includes both GTDS and i.v. granisetron.

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 i.v. granisetron, the mean maximum plasma concentration was reached at 0.6 hours postdose and quantifiable plasma concentrations decreased below the lower limits of quantification by 48 hours in many subjects. As in the GTDS group, the i.v. granisetron group had higher mean granisetron plasma concentrations in women than in men; however, the difference was somewhat smaller in the i.v. 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 postdose, after which plasma concentrations declined.

Pharmacodynamics

Results of analysis of the relationship between plasma concentration and change in QTcF are shown in Fig. 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.

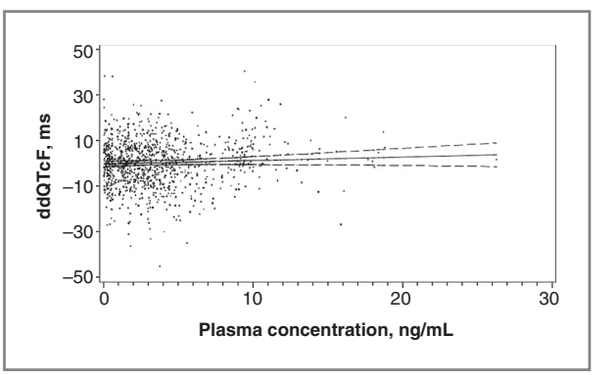

Figure 2. QTcF–plasma concentration relationship for granisetron. Both GTDS and i.v. granisetron data were used to construct the model. The 90% CI bounds are displayed. (Model parameters are shown in Table 4.)

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 i.v. 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 one treatment-emergent adverse event was 53% ($n = 32$) for group 1 (GTDS), 27% ($n = 16$) for group 2 (i.v. granisetron), 45% ($n = 27$) for group 3 (placebo), and 30% ($n = 18$) for group 4 (moxifloxacin). The majority of adverse event 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 i.v. 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 adverse event of headache on day 3 that was considered probably related to treatment and that resolved on the same day.

The majority of adverse events were considered by the investigator to be related to treatment. Table 6 summarizes treatment-related adverse events reported in at least one patient. The most frequently reported adverse event 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 i.v. 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 i.v. granisetron (group 2) and placebo (group 3) and 0% with moxifloxacin (group 4).

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

Discussion

This study shows minimal effect of granisetron, when used in accordance with package labeling, on cardiac repolarization. Although change in QTcF was not statistically significant during treatment with i.v. 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,

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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

Adverse event, *n* (%)	GTDS group 1 (N = 60)	Intravenous granisetron group 2 (N = 60)	Placebo group 3 (N = 60)	Moxifloxacin group 4 (N = 60)
Subjects with at least one 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)

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 i.v. 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 i.v. granisetron, despite it being slightly higher than for GTDS, whereas 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 about 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-HT_3 receptor antagonist antiemetic drugs is inconsistent with regard to QT prolongation, which is classified as a precaution for oral and i.v. formulations of granisetron (10, 11) and a warning for oral ondansetron but not i.v. ondansetron (8, 9), as well as the removal of a warning from the package insert for i.v. palonosetron (12). Furthermore, Roche issued a drug warning separate from the label, indicating that QTc prolongation has been reported for Kytril (i.v. and oral granisetron) and that this medication should be used with appropriate caution (13). Recently, i.v. dolasetron (Anzemet) was contraindicated for CINV because of QT prolongation (6) and, whereas the same warning and precaution about QT prolongation are listed in the labeling of the oral and i.v. 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 conducted 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 i.v. granisetron were as expected: C_{max} was lower for GTDS than for i.v. granisetron (3.63 vs. 4.95 ng/mL, respectively), T_{max} was higher for GTDS (56.08 vs. 0.57 hours), and the AUC_{0-120h} for GTDS was higher than the $AUC_{0-infinity}$ for i.v. granisetron (238.5 vs. 36.87 ng·h/mL). Intersubject variability of pharmacokinetics was high for both GTDS and i.v. granisetron, although lower for GTDS, and exposure was higher in women than in men for both GTDS and i.v. granisetron, although there was considerable overlap in the ranges of individual values.

Our findings suggest that granisetron delivered by the i.v. 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, although this possibility is only weakly supported by pharmacodynamics analyses. Because 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 III trial of GTDS in patients who were receiving multiday moderately or highly emetogenic chemotherapy

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

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 show that GTDS achieved more prolonged therapeutic plasma concentrations of drug than i.v. 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.

Disclosure of Potential Conflicts of Interest

B. O'Mahony is currently an employee of Quintiles Ltd. No potential conflicts of interest were disclosed by the other authors.

Grant Support

This study was sponsored by ProStrakan Pharmaceuticals, Ltd. Editorial support was provided by Peloton Advantage, LLC, funded by ProStrakan, Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 28, 2011; revised February 15, 2012; accepted March 11, 2012; published OnlineFirst March 27, 2012.

References

1. Hesketh PJ. Comparative review of 5-HT3 receptor antagonists in the treatment of acute chemotherapy-induced nausea and vomiting. Cancer Invest 2000;18:163–73.
2. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. Oncologist 2004;9:673–86.
3. International Conference on Harmonisation (ICH). Guidance for industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. [updated 2005 Oct; cited 2011 Jul 13]. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf.
4. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine$_3$ receptor antagonists. Ann Pharmacother 2003;37:1276–86.
5. Keefe DL. The cardiotoxic potential of the 5-HT(3) receptor antagonist antiemetics: is there cause for concern? Oncologist 2002;7:65–72.
6. Anzemet® injection (dolesetron mesylate) [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2011.
7. Anzemet® tablets (dolasetron mesylate) [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2011.
8. Zofran® (ondansetron hydrochloride) tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
9. Zofran® (ondansetron hydrochloride) injection for intravenous use [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2011.
10. Kytril (granisetron hydrochloride) injection, for intravenous use [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2011.
11. Kytril (granisetron hydrochloride) tablets [package insert]. Nutley, NJ: Roche Laboratories Inc.; 2010.
12. Aloxi® (palonsetron HCl) injection for intravenous use [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2009.
13. Sancuso (granisetron transdermal system) [package insert]. Bedminster, NJ: ProStrakan, Inc.; 2008.
14. Howell J, Smeets J, Drenth HJ, Gill D. Pharmacokinetics of a granisetron transdermal system for the treatment of chemotherapy-induced nausea and vomiting. J Oncol Pharm Pract 2009;15:223–31.
15. Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. Support Care Cancer 2011;19:1609–17.
16. Center for Drug Evaluation and Research, Office of New Drugs. Manual of policies and procedures, interdisciplinary review team for QT studies [MAPP 6020.14]. [updated 2007 Oct 16; cited 2011 Aug 18]. Available from: http://www.icardiac.com/downloads/QT%20IRT%20MAPP%206020.14.pdf.
17. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. Ann Noninvasive Electrocardiol 2003;8:343–51.
18. Zhang J, Machado SG. Statistical issues including design and sample size calculation in thorough QT/QTc studies. J Biopharm Stat 2008;18:451–67.
19. FDA Drug Safety Communication: abnormal heart rhythms associated with use of Anzemet (dolasetron mesylate). [updated 2010 Dec 17; cited 2011 Apr 7]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm237081.htm.
20. Buyukavci M, Olgun H, Ceviz N. The effects of ondansetron and granisetron on electrocardiography in children receiving chemotherapy for acute leukemia. Am J Clin Oncol 2005;28:201–4.
21. Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability. Anticancer Drugs 2003;14:739–44.
22. Corrigan BW, Nicholls B, Thakrar B, Lam R, Grosse C, Alianti J, et al. Heterogeneity in systemic availability of ondansetron and granisetron following oral administration. Drug Metab Dispos 1999;27:110–2.
23. Cupissol D, Bressolle F, Adenis L, Carmichael J, Bessell E, Allen A, et al. Evaluation of the bioequivalence of tablet and capsule formulations of granisetron in patients undergoing cytotoxic chemotherapy for malignant disease. J Pharm Sci 1993;82:1281–4.
24. Upward JW, Arnold BD, Link C, Pierce DM, Allen A, Tasker TC. The clinical pharmacology of granisetron (BRL 43694), a novel specific 5-HT3 antagonist. Eur J Cancer 1990;26 Suppl 1:S12–5.
25. Roden DM, Yang T. Protecting the heart against arrhythmias: potassium current physiology and repolarization reserve. Circulation 2005;112:1376–8.
26. Howell J, Mason JW, O'Mahony B, Donachie P. Cardiac safety of a granisetron transdermal system in the treatment of chemotherapy-induced nausea and vomiting [abstract]. In: Proceedings of the MASCC/ISOO Annual International Symposium; 2011 Jun 23–25; Athens, Greece.

Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2785

Clinical Cancer Research

Pharmacokinetics and Repolarization Effects of Intravenous and Transdermal Granisetron

Jay W. Mason, Daniel S. Selness, Thomas E. Moon, et al.

Clin Cancer Res 2012;18:2913-2921. Published OnlineFirst March 27, 2012.