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Thorough QT study of the effect of oral moxifloxacin on QT_c interval in the fed and fasted state in healthy Japanese and Caucasian subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Owing to its potassium channel blocking properties, moxifloxacin is routinely used as a probe to confirm assay sensitivity in thorough electrocardiogram (ECG) studies.
- A meal has been shown to shorten the QT interval and in some instances it may be desirable to use moxifloxacin after a meal which may affect pharmacokinetics (PK) or pharmacodynamics (PD) or both. However there is no published data.
- There is also a paucity of data investigating ethnic differences of the effects of medicines on QT_c.

WHAT THIS STUDY ADDS

- This study defined the difference in the effect of oral moxifloxacin on the QT_c interval in the fed and fasted state in healthy Japanese and Caucasian subjects under the rigorous conditions of a thorough QT (TQT) study.
- The study revealed that the apparent difference in QT_c effects in fed and fasted conditions is the sum of two distinct effects: (i) a meal primarily delayed and reduced the absorption of moxifloxacin and (ii) the QT_c shortening effect of a meal counteracted the QT_c prolonging effect of moxifloxacin beyond that caused by the difference in PK.
- Subtle differences between Caucasian and Japanese subjects were observed in this study but due to the small sample size these differences were not statistically significant. Caucasians were on average heavier than Japanese subjects resulting in differences in drug exposure.

AIMS

The aims of this study were three-fold and were to (i) investigate the effect of food (fasted and fed state) on the degree of QT prolongation caused by moxifloxacin under the rigorous conditions of a TQT study, (ii) differentiate the effects on QT_c that arise from changes in PK from those arising as a result of electrophysiological changes attributable to raised levels of C-peptide [11] offsetting in part the I_{Kr} blocking properties of moxifloxacin and (iii) characterize the QT_cF profile of oral moxifloxacin (400 mg) in healthy Japanese volunteers compared with Caucasian subjects.

METHODS

The study population consisted of 32 healthy non-smoking, Caucasian ($n = 13$) and Japanese ($n = 19$), male and female subjects, aged between 20–45 years with a body mass index of between 18 to 25 kg m^{-2}. Female volunteers were required to use an effective contraceptive method or be abstinent. Subjects with ECGs which were deemed unsuitable for evaluation in a TQT study were excluded. ECGs were recorded in triplicate with subsequent blinded manual adjudication of the automated interval measurements. Electrocardiograms in the placebo arm were recorded twice in fasted and fed condition.

RESULTS

The results demonstrated a substantial change in the typical moxifloxacin effect on the ECG. The effect on $\Delta\Delta QT_c$ in the fed state led to a significant delay and a modest reduction compared with the fasted state correcting both conditions with the corresponding placebo data. The largest QT_cF change from baseline in the fed state was observed at 4 h with a peak value of 11.6 ms (two-sided 90% CI 9.1, 14.1). In comparison, the largest QT_cF change observed in the fasted state was 14.4 ms (90% CI 11.9, 16.8) and occurred at 2.5 h post-dose. The PK of moxifloxacin were altered by food and this change was consistent with the observed QT_cF change. In the fed state plasma concentrations of moxifloxacin were considerably and consistently lower in comparison with the fasted state, and this applied to both ethnicities. The concentration–effect analysis revealed that there was no change in slope and confirmed that the difference in this analysis was caused by a change in the PK profile of moxifloxacin. Comparisons of the moxifloxacin effect in the fed state compared with fasted placebo also revealed a pharmacodynamic effect whereby a meal appears to antagonize the effects of moxifloxacin on the lengths of the QT_c interval.

CONCLUSIONS

Our findings demonstrate that the food effect by itself leads to a shortening of the QT_c interval offsetting in part the effects of a 400 mg single dose of oral moxifloxacin. The typical moxifloxacin PK profile is also altered by food prior to dosing reducing the C_{max} and delays the peak effects on QT_c up to several hours thereby reducing the overall magnitude of the effect and delaying the peak QT_c prolongation. The contribution of the two effects was clearly discernible. Given that moxifloxacin is sometimes given with food in TQT studies, consideration should be given to adequate baseline corrections and appropriate sampling time points. In this study the PK–PD relationship was similar for Japanese and Caucasian subjects in the fed and fasted conditions, thereby providing further evidence that the sensitivity to the QT_c prolonging effects of fluoroquinolones was likely to be independent of ethnicity. The small differences observed between the two subpopulations were not statistically significant. However, future studies should give consideration to formal ethnic comparisons as a secondary outcome parameter as very little is known about the relationship between ethnicity and drug effects on cardiac repolarization.

Introduction

Thorough QT_c (TQT) studies are a well-established method for testing the pro-arrhythmic propensity of drugs. The design of these studies is described in guideline documents and is widely documented the in literature [1]. An indispensable part of any study designed in accordance with the current International Conference on Harmonization (ICH) E14 guidelines is the use of a positive control that can change the QT_c interval in a reproducible manner and therefore can be used to assure assay sensitivity [2, 3]. The QT_c prolonging effects of the anti-bacterial fluoroquinolone, moxifloxacin, have been used in many TQT studies to demonstrate the sensitivity of the assay [4]. In most instances it is used in the fasted state but occasionally it is desirable to administer moxifloxacin in a fed condition. This may alter the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of moxifloxacin. However, there are no published reports on the effects of moxifloxacin on the QT_c interval under fed conditions.

Moxifloxacin is a reversible blocker of the rapid component of the delayed rectifier, potassium current of the cardiac I_{Kr} potassium channel and causes a mean increase of the QT_c interval of 10–14 ms between 2 and 4 h after an oral single dose of 400 mg [4–9]. The ICH E14 guidelines state that a positive control used in a TQT study should cause at least a 5 ms change in the QT_c [3]. According to the ICH E14 Questions & Answers document [3], two approaches are suggested in which a positive control showing an effect 'greater than 5 ms,' or a positive control with an effect 'close to 5 ms,' can be used. Recently we have shown that food produces a QT_c shortening effect [10] correlated closely with the release of C-peptide and blood glucose concentrations [11]. The PK of moxifloxacin is altered if taken after a meal [4, 12]. However there is controversy in the literature with some studies reporting that the PK of moxifloxacin do not change after a meal [13, 14]. It is therefore conceivable that food may alter the effect of moxifloxacin on the QT_c interval in more than one way when given together. However, the interaction between moxifloxacin and the food effect on cardiac repolarization has not been formally investigated.

There are no data on the effect of moxifloxacin on QT_c comparing directly Japanese with Caucasians. Various studies have tried to evaluate differences between ethnicities. Indeed, there is ample evidence that both the PK and/or PD of various drugs differ when comparing different ethnicities [15, 16]. We have previously investigated differences in QT_c response to levlofloxacin between Caucasian and Japanese subjects and found that the slope of levofloxacin for Japanese subjects was approximately 74% of that observed in Caucasian subjects but due to the small sample size and the setup of this investigation, there was no statistically significant difference in the sensitivity between ethnicities [17]. However, it should be noted that in comparison with moxifloxacin (IC_{50}, 129 μM), levofloxacin is a very weak blocker of I_{Kr} (IC_{50}, 915 μM) [18] and so it is also possible that that differences with regard to ethnicity on the QT_c cannot be demonstrated at tolerable dose levels i.e. would only become apparent at much higher plasma concentrations. Reports on electrocardiographic and ethnic differences are sparse and largely inconclusive. These differences are not thought to be of any clinical relevance. In addition, ICH E14 states that racial effects are not to be expected and the results of a typical TQT study are not formally analyzed in terms of ethnic differences. Equally, given the lack of evidence to either support or discourage specific investigations in different ethnicities, further studies comparing ECG effects, are desirable [15]. The ICH E5 guideline provides for formal assessments of ethnic differences in drug response and safety. Notably, bridging ECG studies performed in a similar way would allow for meaningful comparisons where ethnicity would be the only variable. In this respect, this is the first study to investigate the effect of moxifloxacin on the QT interval in healthy Japanese and Caucasian subjects within the same study and site.

Methods

Study design

This study was designed as an open-label, randomized, placebo-controlled, crossover trial that evaluated the effect of a 400 mg oral dose of moxifloxacin in fed and fasted conditions to a baseline and a placebo treatment. Subjects participating in the study attended for screening, two treatment periods (periods 1 and 2) of 4 assessment days each and a follow-up visit (Table 1). Data obtained on study days 1 and 2 compared the ECG effects of different types of food and placebo. These results have been presented elsewhere [10]. Each period consisted of a baseline ECG day (day −1) and treatment days (days 1–3). Moxifloxacin was given in either the fed or fasted condition, on day 3 of each study period. The two periods were separated by at least 3 days to allow for the effects of moxifloxacin to wash-out. No wash-out was required between the other treatments investigated. The ECG and samples for PK and PD analysis on the treatment days were taken at the corresponding clock time points as on the baseline days. Each subject received all treatments and all the comparisons between treatment effects were made intra-individually reducing the anticipated variability and thereby reducing the sample size.

Breakfasts were provided 30 min prior to the scheduled dosing time and were to be consumed 10 min before dosing (time 0). Subjects were served lunch (7 h post-dose), dinner (11 h post-dose) and a snack (13.5 h post-dose). Two types of breakfasts were used, one was a continental breakfast and rich in carbohydrates (used in this publication) and the other was a calorie reduced FDA standard breakfast (data presented elsewhere [10]) which

Table 1
Summary of study design

Period 1 Day –1	Day 1	Day 2	*Day 3	Washout Minimum of 3 days	Period 2 Day –1	Day 1	Day 2	*Day 3
P	P	I	M		P	B	F	M + B
	I	B	M			F	P	M + B
	B	F	M			P	I	M + B
	F	P	M			I	B	M + B
	P	I	M + B			B	F	M
	I	B	M + B			F	P	M
	B	F	M + B			P	I	M
	F	P	M + B			I	B	M

For completeness, the entire study design is presented but only *day 3 was part of this study. The data from days 1 and 2 were reported elsewhere [11].
B, high carbohydrate breakfast (>70% carbohydrates); F, calorie reduced FDA standard breakfast; I, insulin + glucose (clamp); M, moxifloxacin; P, placebo.

was low in carbohydrates and rich in fat and not given prior to the moxifloxacin administration.

The study (EudraCT: 2011–002423-17, NCT01642485) was approved by a National Health Service (NHS) Research Ethics Committee (London Surrey-Borders, UK) and the Medicines and Healthcare products Regulatory Authority (MHRA) and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

ECG assessment and QT_c evaluation

Twelve-lead ECGs were recorded using a MAC1200® (500 samples s^{-1}, 4.88 μV amplitude resolution, GE Healthcare, Milwaukee, WI, USA) recorder connected via a fixed network connection to the MUSE® Cardiology Information System (MUSE). All ECGs recorded during the study were stored electronically on the MUSE information system. Only ECGs recorded electronically at a stable heart rate were valid for QT interval measurements. Simultaneous 12-lead Holter ECG recordings were taken from pre-dose to 6 h post-dose for later analysis (data not presented).

Twelve-lead ECG recordings were made at the following time points, pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 6.0 h post-dose on days –1, 1, 2, and 3 of each period after the subjects had been resting in a supine position for at least 10 min. Clinical staff ensured that subjects were awake during all ECG recordings to avoid autonomic QT_c changes occurring during sleep. The use of a semi-permanent skin marker was used to ensure consistent placement of the leads for consecutive study days. At each time point, the ECGs were recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates were performed at approximately 1 min intervals.

ECG analysis

Each electronic ECG data file contained the ECG data as well as the result of the automated ECG analysis performed by the Marquette® 12SL™ ECG Analysis Program (MEAP), software which handles the data within each of the ECG recorders.

All ECGs and their associated automated interval measurements were subsequently reviewed by qualified cardiologists following one of the methods listed in the ICH E14 Guidance for Industry document [2] and ICH E14 Implementation Working Group Questions and Answers document [4] before any of the ECGs were used for the subsequent statistical analyses. The manual adjudication process applied in this study is also referred to in the ICH guidance and relevant literature as 'manual over-read' ECG measurements. All ECGs recorded were manually adjudicated by a competent cardiologist to review and document.

The QT interval, RR interval and heart rate, PR interval and QRS duration, the presence or absence of U-waves, quantitative and qualitative ECG variations were assessed by cardiologists with extensive experience with manual on-screen over-reading using electronic callipers using the commercially available MUSE® in its latest version to correct any implausible readings presented by the automated process. For all study ECGs, the over-reading cardiologists were blinded to time, date, treatment and any data identifying the subject. All ECGs pertaining to an individual volunteer were over-read by the same cardiologist to ensure consistency across all treatments. If manual adjustments of the automated measurement became necessary, a second cardiologist confirmed the assessment. Any disagreement between first and second reader was adjudicated by a third and most senior cardiologist.

Fridericia's heart rate correction (QT_cF) was used for adjustment of heart rate changes in line with our previous publication [10], where we showed that QT_cF was in good agreement with individual heart rate corrections whereas QT_cB was grossly overcorrecting as a meal consistently causes heart rate increases of up to 10 beats min^{-1}.

Statistical analysis

The primary analysis was based on the change of QT_cF from the average of all baseline readings. A confirmatory analysis was based on the average of QT_cF over all time points between and including 2 and 4 h. Descriptive analyses for each time point separately were also performed. The confirmatory part of the primary analysis followed a hierarchical test procedure testing the following null hypotheses in fixed order: (i) there is no difference between carbohydrate rich breakfast and placebo (test for difference), (ii) there is no difference between calorie-reduced FDA breakfast and placebo (test for difference), (iii) the prolongation under the euglycaemic hyperinsulinaemic clamp [11] at 1:30 h is ≥10 ms (test for non-inferiority), (iv) the absolute difference between the effect of moxifloxacin given in fed and fasted conditions is ≥10 ms (test for equivalence) and (v) there is no difference in the degree of QT_c prolongation after moxifloxacin (given in fasted state) and placebo between Caucasians and Japanese (test for difference). The results of the first three tests have been published elsewhere [11]. They are reported in this paper to assess the influence of multiplicity to the results.

A linear mixed model with sequence, day, period, gender, ethnicity and treatment as fixed effects, and baseline as covariate was adapted, with subject (nested in sequence, gender and ethnicity) as random effect. Two-sided 90% confidence intervals (CIs) for the difference between each treatment and placebo and between the two types of breakfast were derived. All subjects in the safety dataset who had valid ECG data for time points during days 1–3 of periods 1 and 2 were included in the primary analysis set. All statistical analyses were performed using R version 2.13.0 [19] or later. The descriptive per time point analysis followed the same lines.

Linear modelling of the effect of the moxifloxacin plasma concentration on the difference to placebo only or placebo plus breakfast of the change from average baseline was also performed in an exploratory way. The basic model used fed status as factor, plasma concentration and its interaction with fed status as covariates and an intercept, plasma concentration and its interaction with fed status as random effects with subject as grouping [4]. In addition, gender and ethnicity and their interaction with moxifloxacin concentration were entered as fixed effects into the model. Model fit was investigated by using normal QQ-plots of the residuals. Estimates of slopes and of the effect at a number of concentrations were given together with their 90% two-sided confidence intervals (CIs).

Results

Subject demographics

A total of 32 subjects were included in the study. Subject demographics are presented by descriptive statistics in Table 2.

Confirmatory analysis

The first three null hypotheses of the confirmatory part of the analysis could all be rejected. However, the subsequent null hypothesis of equivalence of the average effect of moxifloxacin on QT_cF in fasted and fed state could not be rejected, pointing to a marked difference between the two feeding states.

Comparison of the effect of a single oral 400 mg dose of moxifloxacin on QT_cF, given after a meal and given after fasting overnight

The results demonstrated a substantial delay of the effect on QT_c in the fed state compared to the fasted state. The largest QT_cF change from baseline in the fed state (Figure 1) was observed at 4 h with a peak value of 11.6 ms (two-sided 90% CI 9.1, 14.1). In comparison, the largest QT_cF change observed in the fasted state was 14.4 ms (90% CI 11.9, 16.8) and occurred at 2.5 h post-dose as described previously [10]. The values for each time point are presented in Table 3. The QT_cF change was calculated using placebo data collected after a breakfast identical to that used prior to the moxifloxacin administration, thereby eliminating any effect the meal itself may have directly on QT_cF [10]. Therefore, the QT_cF change observed and

Table 2

Subject demographics

Ethnicity	Gender	*n*	Age (years)	SD	Height (cm)	SD	Body weight (kg)	SD
Caucasian	All	**13**	**25.6**	**4.7**	**172.8**	**9.7**	**65.1**	**7.4**
	Male	7	25.0	4.5	178.4	6.2	68.3	7.1
	Female	6	26.3	5.2	166.3	9.1	61.4	6.4
Japanese	All	**19**	**27.6**	**3.3**	**167.2**	**7.2**	**58.0**	**5.7**
	Male	11	26.6	3.3	171.2	5.2	59.8	5.4
	Female	8	29.0	3.1	161.6	5.8	55.5	5.4
Total		**32**	**26.8**	**4.0**	**169.5**	**8.6**	**60.9**	**7.3**

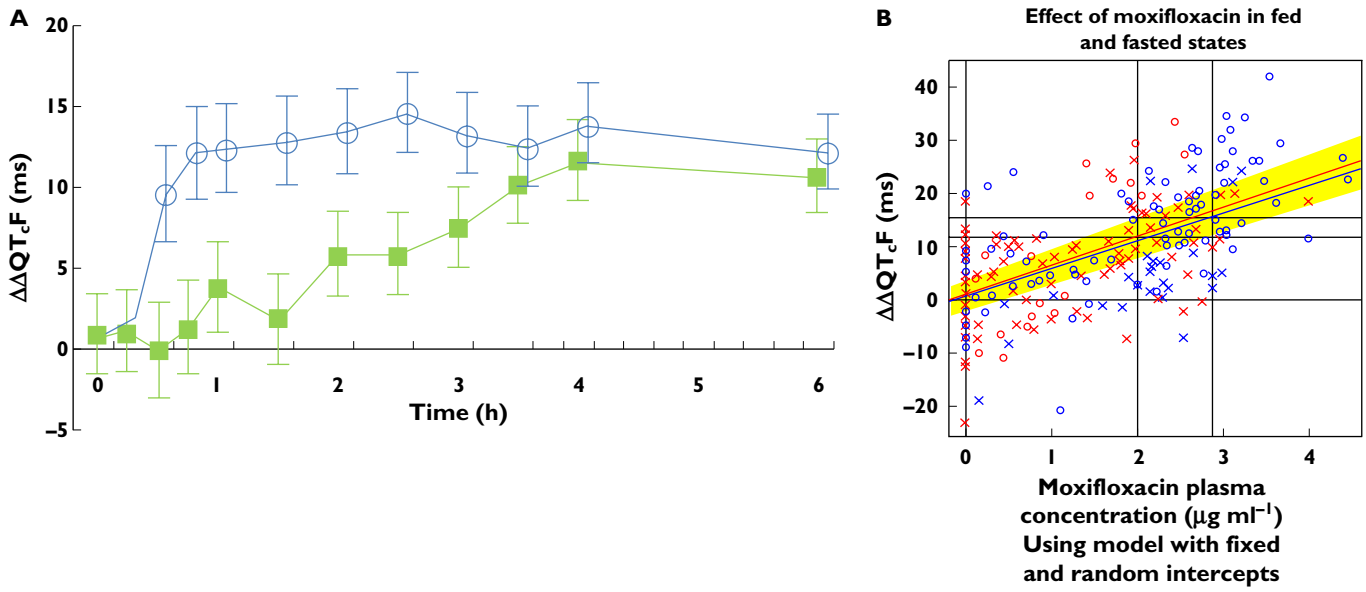

Figure 1

Changes in QT_cF after a 400 mg dose of moxifloxacin with and without food ($n = 32$). The time course relationship comparing the moxifloxacin effects with and without food (A). The direct effects of food on QT_c are removed as food is also given in both treatment arms where it would have had the same effects on QT_c. The PK data (Figure 2) shows a delay and reduction in absorption (B). The PK–PD relationship is displayed in (B) and demonstrates that the delayed and somewhat lower effect of moxifloxacin is entirely driven by the altered PK of the drug. The regression lines are derived from a linear mixed effects model with concentration as covariate, ethnicity and gender and their interactions with concentration as fixed effects and random intercept and slope by subject. The vertical lines give the 95% CI for the predicted effect at the geometric mean C_{max} in the fed and fasted states respectively. ■, effect on QT_cF (fed estimate); ⊖, effect on QT_cF (fasted estimate); ○, female; ×, male; —, fed; —, fasted

Table 3

Changes in QT_cF by time point after a single dose of 400 mg moxifloxacin in the fed and fasted state

Time (h)	Fasted estimate (ms) (90% CI)		Fed estimate (ms) (90% CI)	
0:00	**0.7**	(–1.7, 3.2)	**0.8**	(–1.6, 3.3)
0:25	**1.7**	(–0.8, 4.2)	**1**	(–1.5, 3.6)
0:50	**9.3**	(6.3, 12.3)	**–0.1**	(–3.1, 2.8)
0:75	**11.9**	(9, 14.7)	**1.2**	(–1.6, 4.4)
1:00	**12.1**	(9.4, 14.9)	**3.8**	(1, 6.5)
1:50	**12.6**	(9.9, 15.3)	**1.8**	(–1, 4.5)
2:00	**13.2**	(10.5, 15.8)	**5.8**	(3.2, 8.4)
2:50	**14.4**	(11.9, 16.8)	**5.8**	(3.3, 8.3)
3:00	**13**	(10.6, 15.5)	**7.4**	(5, 9.9)
3:50	**12.2**	(9.8, 14.7)	**10.1**	(7.7, 12.6)
4:00	**13.6**	(11.2, 16.1)	**11.6**	(9.1, 14.1)
6:00	**11.9**	(9.6, 14.2)	**10.6**	(8.3, 12.9)

Effect of Moxifloxacin on change from average baseline of QT_cF, corrected for time matched control – fasted and fed placebo respectively, together with two sided 90% confidence intervals. The table gives the numeric values (in bold) to Fig 1A.

displayed in Figure 1 represents a change in QT_cF caused by the altered PK of moxifloxacin in blood if administered after a meal.

Moxifloxacin plasma concentration and changes in QT_cF in fed and fasted condition

The moxifloxacin plasma concentration time course (Figure 2) revealed that the PK of moxifloxacin were altered

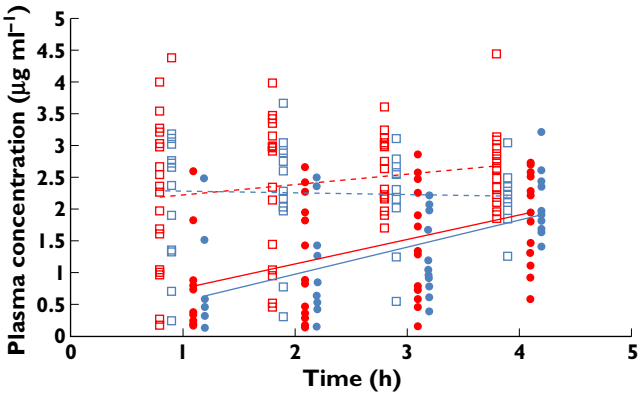

Figure 2

Individual plasma concentrations of 400 mg moxifloxacin in fasted and fed state. The individual moxifloxacin concentrations, plotted by ethnicity and feeding status showing the delay in absorption when moxifloxacin is taken 10 min after finishing a carbohydrate rich breakfast. □, moxifloxacin 400 mg fasted (Japanese); ●, moxifloxacin 400 mg + breakfast (Japanese); □, moxifloxacin 400 mg fasted (Caucasian); ●, moxifloxacin 400 mg + breakfast (Caucasian)

by food and this change in PK is consistent with the observed QT_cF change. In the fed state plasma concentrations of moxifloxacin were considerably and consistently lower in comparison with the fasted state, and this applied to both ethnicities. The concentration effect analysis

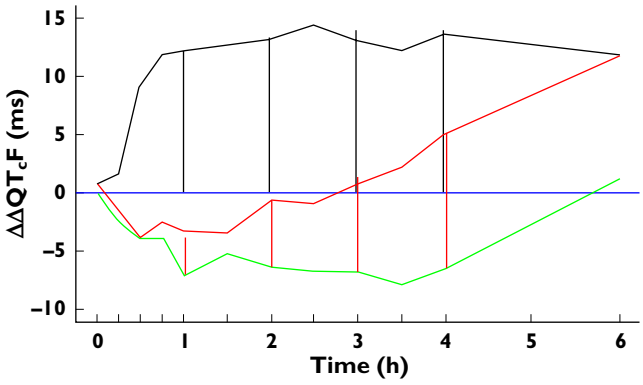

Figure 3

Pharmacokinetic predicted effects of food, (fed and fasted) on the moxifloxacin effect on the QT_cF interval. Time matched mean changes from placebo (fasting placebo was subtracted from fed moxifloxacin to reveal the PD contribution of food). The vertical bars give the predicted effect of moxifloxacin on $\Delta\Delta QT_cF$ under a common model for the fed and fasted state for time points for which moxifloxacin concentrations were measured. The observed effect of moxifloxacin in the fasted state is the difference between the black and the blue curve. The combined effect of moxifloxacin plus a meal is shown by the red line. The effects match the vertical bars, i.e. the model predicts the mean effect over time. ——, moxifloxacin fasted; ——, moxifloxacin fed; ——, breakfast; ——, placebo.

(Figure 1B) shows that there was no change in slope confirming that the difference in this analysis was essentially caused by a change in the PK profile of the fed and fasted conditions.

Moxifloxacin C_{max} and AUC(0,t) in Japanese and Caucasian subjects

Moxifloxacin plasma concentration parameters observed in the Japanese subjects were found be higher than in the Caucasian subjects. The mean C_{max} for moxifloxacin was found to be 3.15 ± 0.59 μg ml^{-1} in Japanese subjects and 2.66 ± 0.74 μg ml^{-1} in Caucasian subjects. Concomitantly, AUC(0,*t*) was also marginally higher in Japanese subjects with a value found to be 8.42 ± 2.47 μg ml^{-1} h in comparison with 8.05 ± 2.89 μg ml^{-1} h for Caucasian subjects.

Differences to time matched fasted placebo and pharmacokinetic-predicted effects

Figure 3 shows the superposition of PK and PD effects of food on the effect of moxifloxacin on QT_cF. The full effect of giving moxifloxacin after a meal is a significant attenuation of the QT_cF prolonging effects of moxifloxacin. As seen in Figure 3, the QT_cF only started to increase 3 h following the administration of a 400 mg moxifloxacin tablet. After 4 h, the QT_cF interval increased by about 5 ms and only at the 6 h time point did QT_cF values that were observed in the fed state became similar to those in fasted state. This much larger effect is a combined effect of the change in the PK of moxifloxacin as described above leading to a delayed and reduced prolongation of QT_c plus the QT_c shortening effect of raised levels of C-peptide released after a meal.

Effect of moxifloxacin on QT_cF in the Japanese and Caucasian subjects

Both ethnicities showed prolongation in the mean QT_cF interval after a single oral 400 mg moxifloxacin dose in the fasted state compared with placebo (Figure 4).

Greatest change from baseline in the fasted state The greatest change from baseline (20 ms, two-sided 90% CI 14.9, 25.1) was observed in the fasted state for Japanese subjects at 3 h (Figure 4A).

Greatest change from baseline in the fed state The greatest change from baseline (13.7 ms; two-sided 90% CI 9.9, 17.5) was observed in the fed state for Caucasian subjects at the 4 h time-point (Figure 4B).

PK-$\Delta\Delta QT_cF$ relationship (fed/fasted) for Japanese and Caucasian subjects

The relationship between QT_cF and the moxifloxacin plasma concentration in Japanese and Caucasian subjects in the fed and fasted state is shown in Figure 5. An increase in plasma moxifloxacin concentration was associated with QT_cF prolongation in both the Japanese and Caucasian subjects. This relationship was similar for both ethnicities. More specifically, the intercept was below 1 ms in magnitude for both ethnicities and the slopes differed by less than 10%. Neither the difference between slopes nor that between intercepts for the two groups was statistically significant and the 95% CI for the difference in slopes was below 2 ms μg^{-1} ml, i.e. below 40% of the slope. The predicted difference between ethnicities at the geometric mean C_{max} was 1.4 ms, with a 95% two-sided confidence interval of (–2.5, 5.5). Overall, in statistical terms the slopes did not differ between the fed and fasted state.

C_{max}, t_{max} and corresponding $\Delta\Delta QT_cF$ effect at t_{max} of moxifloxacin

Values of C_{max}, $\Delta\Delta QT_cF$ and t_{max} of moxifloxacin in the fed and fasted condition are shown in Table 4. These findings together with the PK data displayed in Figure 2, reveal that in the fasting condition, the moxifloxacin plasma concentrations and effects on QT_cF for Caucasians do not change much over the time interval 1–4 h post-dosing, indicating that no clear systematic effect on t_{max} can be seen in this condition. Caution should be applied to the interpretation of these results because of the wide confidence intervals, particularly in the subgroups.

Discussion

The effect of a meal on QT_cF and the interaction of moxifloxacin

The primary purpose of this study was to characterize the QT_cF effect curve of a single oral dose of moxifloxacin

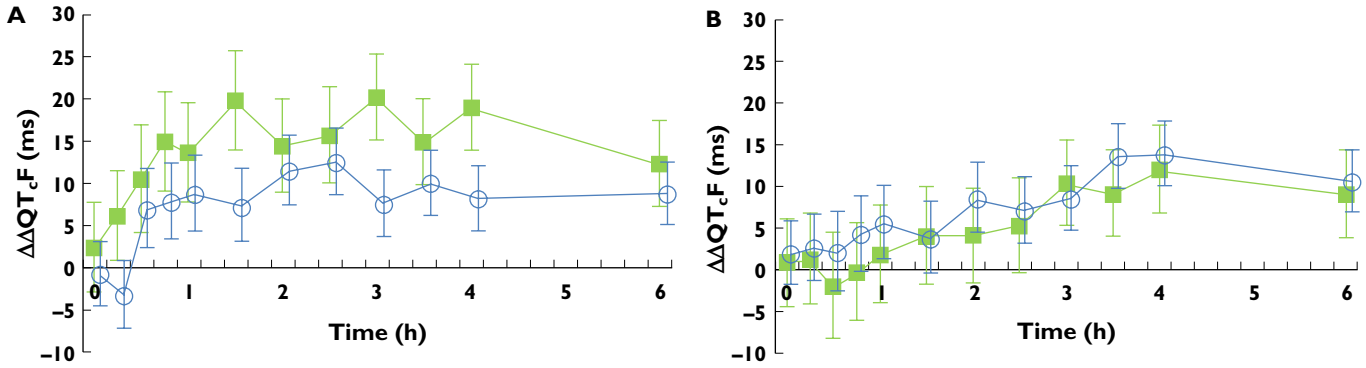

Figure 4

ΔΔQT$_c$F in fasted and fed state in healthy Japanese and Caucasian subjects. The difference between the two curves represents the effect of the moxifloxacin on QT$_c$F in Japanese and Caucasian. A) shows the time course relationship in the fasting condition and B) after breakfast (fed). (A) —■—, fasted Japanese; —○—, fasted Caucasian; (B) —■— fed Japanese; —○— fed Caucasian

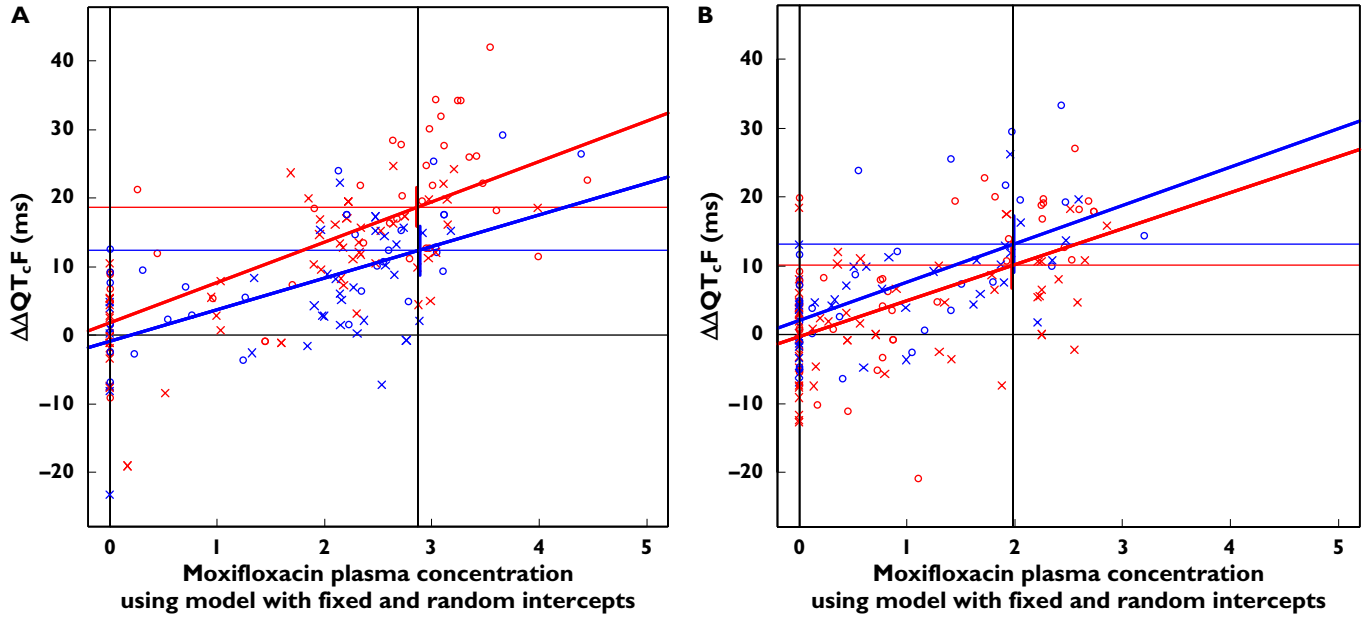

Figure 5

PK-ΔΔQT$_c$F relationship (fed/fasted) for Japanese and Caucasian subjects. The PK–PD relationship by ethnicity: Japanese volunteers show a slightly steeper dose–response curve than Caucasian volunteers in the fasted state (A). However, this is reversed in the fed state (B). In this study, the sample size was small and the effect was likely to have been caused by random effect owing to the small sample size. ○, female; ×, male; ——, Japanese; ——, Caucasian

when given with food to the well characterized QT$_c$F effects in the fasting condition. A further important purpose of the study was to ascertain whether and if so, how, the effect of a meal with a corresponding rise in C-peptide on the QT$_c$F interval may interact with the effects of an I_{Kr} channel blocker such as moxifloxacin. In a study by Bloomfield *et al.* [12] a transient decrease in the change in QT$_c$ from baseline at 5 and 6 h post-dose in both the moxifloxacin and placebo treatment groups was observed, suggesting that food may be responsible for attenuating the QT$_c$F prolongation caused by moxifloxacin. This could suggest that food might have an effect which would go beyond the alterations of PK by the modification of absorption of moxifloxacin as the meal was given 4 h after moxifloxacin. Our findings show that the typical moxifloxacin profile is changed significantly if given after a meal. When comparing the effect of the fed and fasted states, it is apparent that it is not so much the size of the maximum effect that differs between the two states but rather that there is a

Table 4

Group C_{max}, t_{max} and QT_cF effect at t_{max} of moxifloxacin

	Fasted Concentration Mean (95% CI)	t_{max}	$\Delta\Delta QT_cF$ at t_{max} Mean (95% CI)	Fed Concentration Mean (95% CI)	t_{max}	$\Delta\Delta QT_cF$ at t_{max} Mean (95% CI)
All	2.46 (2.26 2.66)	4 h	13.70 (10.90 16.50)	2.02 (1.81 2.23)	4 h	11.50 (8.00 15.10)
Caucasian	2.28 (1.59 2.97)	1 h	9.00 (3.20 14.70)	2.05 (1.76 2.34)	4 h	13.70 (8.20 19.20)
Japanese	2.62 (2.33 2.91)	4 h	17.30 (13.90 20.60)	2.00 (1.69 2.31)	4 h	10.10 (5.10 15.10)
Male	2.40 (2.24 2.57)	3 h	10.80 (6.80 14.70)	1.89 (1.62 2.16)	4 h	9.70 (6.10 13.30)
Female	2.66 (2.26 3.06)	4 h	15.70 (10.60 20.70)	2.19 (1.85 2.53)	4 h	13.90 (6.80 21.10)

Illustration of the results of the concentration–effect analysis: The maximum of the mean concentrations of moxifloxacin and the time of its occurence are given by sub group together with the effect of moxifloxacin on QT_cF ($\Delta\Delta QT_cF$) at this timepoint and a descriptive 95% CI for both the fed and fasted conditions. There is good alignment between concentrations and effects across the two conditions. The only exception is for Caucasians in fasted state. It should be noted that this is the only maximum that occurs already at 1 h.

significant delay of the peak effect in the fed state. The differences in plasma concentrations of moxifloxacin in the fed and fasted condition infer that food reduces the plasma concentration of moxifloxacin, which in turn alters its effect on the QT_cF interval. This finding is consistent with that reported by Florian *et al*. [4], whereby significantly higher mean C_{max} values of 3085 ng ml^{-1} were observed when moxifloxacin was administered in the fasted state compared with C_{max} in subjects who received a meal within 3 h of moxifloxacin administration (2668 ng ml^{-1}), indicating a decreased rate of absorption when moxifloxacin is ingested with food. It has been reported that the effects of moxifloxacin on the QT_c interval are proportional to plasma concentrations and these are influenced by the dose, gender and the body weight of the person receiving the dose. This is consistent with our findings (Table 4) and shows that females have a higher $\Delta\Delta QT_cF$ in the fed and fasted state in comparison with males. This difference was small and would only become statistically significant when several hundred subjects are used [4].

In this study, the concentration–response analysis revealed that the differences seen in QT_cF in Japanese and Caucasian subjects can be fully explained by differences in moxifloxacin PK due to the demographics of the population. Indeed, Japanese subjects have slightly higher plasma concentrations of moxifloxacin in the fed state and therefore a greater QT_cF prolongation. We have reported previously [20] that the effect of moxifloxacin on the QT_cF interval is greater in females. However this apparent difference is due to a lower body weight, resulting in higher plasma concentrations of moxifloxacin. The concentration–effect slope (or sensitivity) for both genders is also almost identical suggesting that the sensitivity to the I_{Kr} blocking properties of moxifloxacin is the same in both genders.

A study by Lettieri *et al*. [13] which investigated the effect of food using moxifloxacin has demonstrated that the PK of 400 mg oral moxifloxacin was unchanged by food. In their study, the area under the concentration–time curve was almost identical in the fed and fasted conditions (37.7 and 38.5 mg l^{-1} h, respectively), and only a 10% decrease was observed in the C_{max}. In addition, another study has shown that moxifloxacin PK only marginally changed when 400 mg oral dose was administered after eating a standard American breakfast with high fat and calorie content [14]. The authors described a slightly lower peak concentration and unchanged area under the curve. It could be reasoned that in these studies [13, 14] meals of a different composition were used and, therefore, salient observations might not have been observed. Florian *et al*. [4], have suggested that it takes approximately 30 min for the changes in QT_cF values to equilibrate with changes in plasma concentrations of moxifloxacin. This finding is consistent with the earlier observation where the maximum effect is typically within the time interval of maximum moxifloxacin plasma concentration [21], and only one study has reported that peak plasma moxifloxacin concentrations are poorly correlated with peak changes in QT_cF prolongation [22]. In summary, our findings show that the typical moxifloxacin PK profile is altered by food prior to dosing and delays the peak effects on QT_c up to several hours thereby reducing the overall magnitude of the effect.

When calculating the changes in QT_cF using placebo data obtained in a baseline condition, then a clear addition of the two important effects emerge:

1 The alteration of the plasma PK with subsequent reduction in the QT_cF effect and
2 The QT_cF shortening effects of C-peptide following a meal.

The cause for the reduction of QT_cF is not well understood. There is no indication that a meal itself alters the I_{Kr} channel inhibition induced by moxifloxacin. We have described that a relationship exists between raised C-peptide concentrations and a carbohydrate rich meal [11], but it remains unclear whether this is due to the stimulation of Na^+/K^+ ATPase by C-peptide by the activation of the protein kinase C (PKC) and mitogen activated protein (MAP) kinase pathway as recently observed in primary human renal tubular cells [23] or whether this effect is an indirect one through mechanisms as yet unknown. However, this paper shows that the two effects are distinguishable and that a meal by itself will reduce the QT_cF prolonging effects of moxifloxacin even after taking into account the effect of a meal on PK.

PK–PD relationship between Japanese and Caucasian subjects

The sub-population analysis in this study revealed subtle differences but overall give no indication for statistically significant differences in QT_c-prolonging effect between Japanese and Caucasian subjects. In fact, the CI for the predicted difference at mean C_{max} makes it unlikely that there is a large difference which would be of clinical relevance. As shown in Figure 5, the Japanese subjects showed a greater apparent sensitivity to the QT_c prolonging effects of moxifloxacin in the fasted state but the effect was reversed in the fed state. The PK concentrations for Japanese subjects shown in Figure 2 are marginally higher in both thefed and fasted state. However, the QT_cF effect following 400 mg moxifloxacin was clearly greater in the Japanese subjects compared with Caucasians in the fasted state and again reversed in the fed state as shown in Figure 4. A possible explanation for this finding could be that the Japanese subjects are more susceptible to the attenuating effects of C-peptide after a meal.

We reiterate that we found no statistically significant difference in the change in QT_cF between ethnicities. Furthermore, it is important to note that the change in the QT_cF for a single dose of moxifloxacin in this study was slightly higher than previously reported [24]. Our concentration–response data are in agreement with the observations made by Sugiyama *et al*. [17] i.e. the QT_cF and PK relationship suggests that there is no statistically significant difference in the slopes between Japanese and Caucasian subjects. The sample size used in this study was small and therefore any differences between Japanese and Caucasian subjects presented in this paper should be treated as exploratory as a much larger data set involving several hundred subjects would be required to obtain a definitive result pertaining to ethnic differences. Our findings based on the confirmatory and concentration–effect analysis show that any difference between ethnicities is largely and quite possibly only attributable to differences in plasma concentrations and not differences in sensitivity to the I_{Kr} blocking properties of moxifloxacin, i.e. comparable with the apparent gender differences in QT_c response as reported in the literature [20].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

The authors made the following contributions: Jorg Taubel designed the study and drafted the manuscript for this publication, Georg Ferber performed all statistical analyses, Ulrike Lorch was the Prinicipal Investigator and conducted the clinical part of the study, Velislav Batchvarov and Irina Savelieva manually adjudicated all ECG data and A. John Camm led the peer review. All authors reviewed the paper and provided their input. We thank D. Djumanov for his contribution to manage the ECG data and J. Singh for re-editing.

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