

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.

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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 ΔΔQT_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.