Moxifloxacin effect on QTc interval in the fed and fasted states in Thorough QT studies

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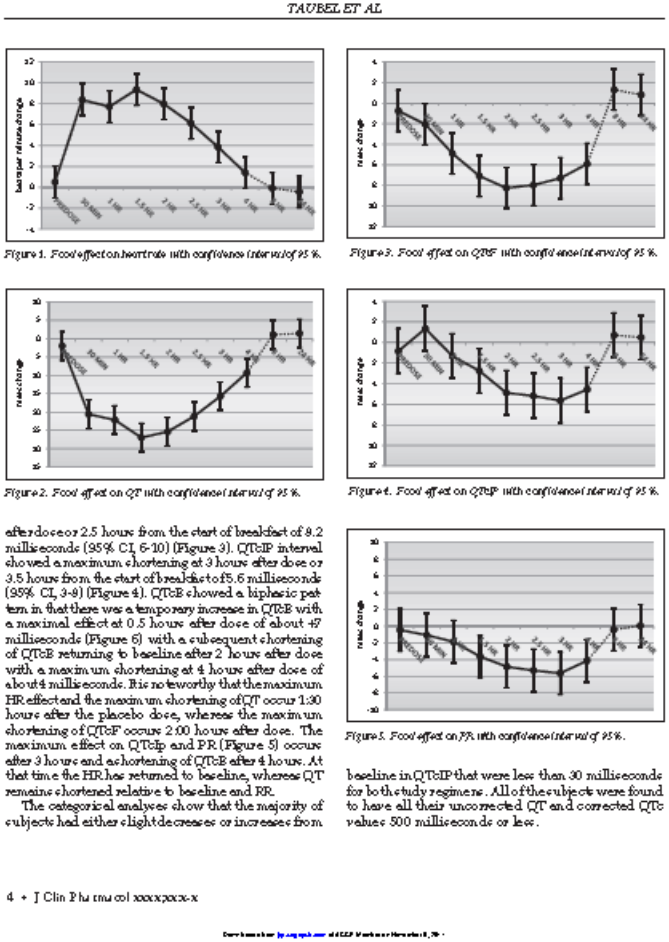
A meal has a profound effect on QTc



TAUBEL ET AL

Figure 1. Food effect on heart rate with confidence interval of 95 %.

Figure 3. Food effect on QTcF with confidence interval of 95 %.

Figure 2. Food effect on QT with confidence interval of 95 %.

Figure 4. Food effect on QTcIP with confidence interval of 95 %.

after dose or 2.5 hours from the start of breakfast of 9.2 milliseconds (95% CI, 6-10) (Figure 3). QTcIP interval showed a maximum shortening at 3 hours after dose or 3.5 hours from the start of breakfast of 5.6 milliseconds (95% CI, 3-9) (Figure 4). QTcB showed a biphasic pattern in that there was a temporary increase in QTcB with a maximal effect at 0.5 hours after dose of about 47 milliseconds (Figure 6) with a subsequent shortening of QTcB returning to baseline after 2 hours after dose with a maximum shortening at 4 hours after dose of about 4 milliseconds. It is noteworthy that the maximum HR effect and the maximum shortening of QT occur 1:30 hours after the placebo dose, whereas the maximum shortening of QTcF occurs 2:00 hours after dose. The maximum effect on QTcIp and PR (Figure 5) occurs after 3 hours and a shortening of QTcB after 4 hours. At that time the HR has returned to baseline, whereas QT remains shortened relative to baseline and RR.

The categorical analyses show that the majority of subjects had either slight decreases or increases from baseline in QTcIP that were less than 30 milliseconds for both study regimens. All of the subjects were found to have all their uncorrected QT and corrected QTc values 500 milliseconds or less.

Figure 5. Food effect on PR with confidence interval of 95 %.

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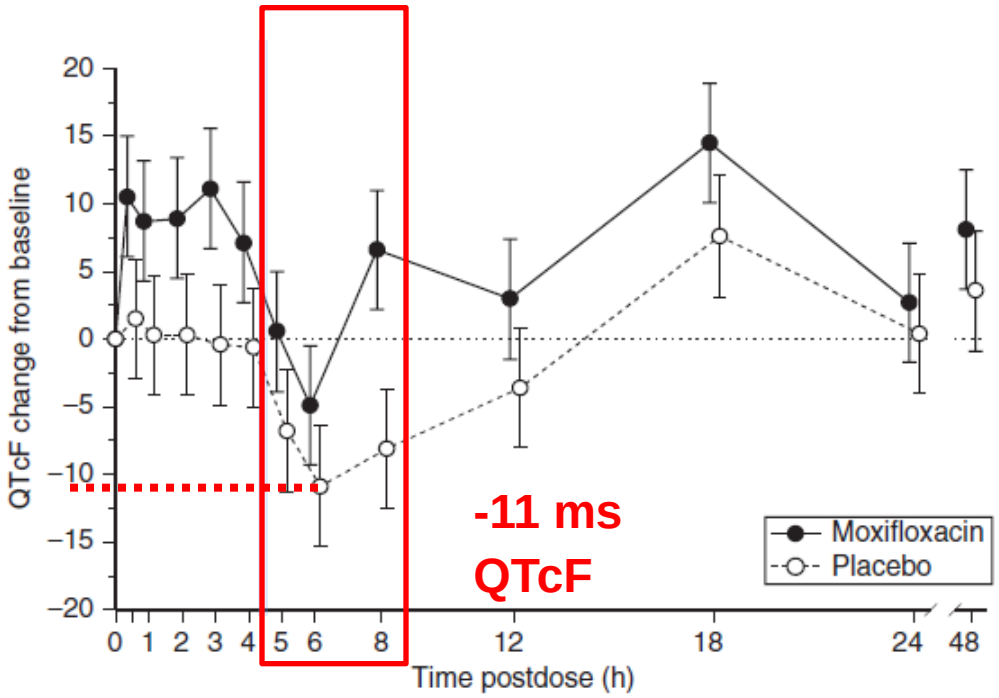
1. Shortening of the QTc interval
2. Similar result QTcF/QTcI
3. Prolongation of QTcB for maximal two hours
4. We speculated that the effect may be caused by a release of c-peptide, more likely than autonomic.

Bloomfield et al. 2008

The Effect of Moxifloxacin on QTc and Implications for the Design of Thorough QT Studies

DM Bloomfield[1], JT Kost[2], K Ghosh[3], D Hreniuk[1], LA Hickey[3], MJ Guitierrez[4], K Gottesdiener[1] and JA Wagner[1]

Figure 4 illustrates the change in QTc from baseline (PDB) brought about by treatment. Moxifloxacin appears to be associated with a ~10 ms increase in QTc CFB, which becomes evident from the first measurement at 30 min and persists over the first 4 h after the dose. In contrast, the mean change in QTc interval associated with placebo over this same 4-h period remained close to zero. Interestingly, there is a transient decrease in the change in QTc from baseline at 5 and 6 h after the dose, similar in both the moxifloxacin and placebo treatment groups. This drop in QTc was associated with small but consistent increases in heart rate that occurred following the meal (which was given to all subjects 4 h after the dose). A secondary increase in QTc appears after 6 h, persisting through 24 h.



Hypothesis

- We wanted to characterise the QTcF profile of oral moxifloxacin in fed and fasted state

  and

  whether the effect of a meal on QTcF would counteract the effects of an ion channel blocker such as Moxifloxacin

Study design

- The study was an open-label, randomised, placebo-controlled, crossover trial that
- evaluated the effect of different meals on the QT/QTc interval of the ECG using a single 400 mg dose of moxifloxacin in
- fed and fasted conditions in
- 32 non-elderly healthy male and female

Study design

- Cross over study in 32 subjects
- Each 3 test days were preceded by an identical baseline day

Period 1				Washout*	Period 2			
Day -1	Day 1	Day 2	Day 3		Day -1	Day 1	Day 2	Day 3
P	P	I	M	Minimum of 3 days	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

Study population

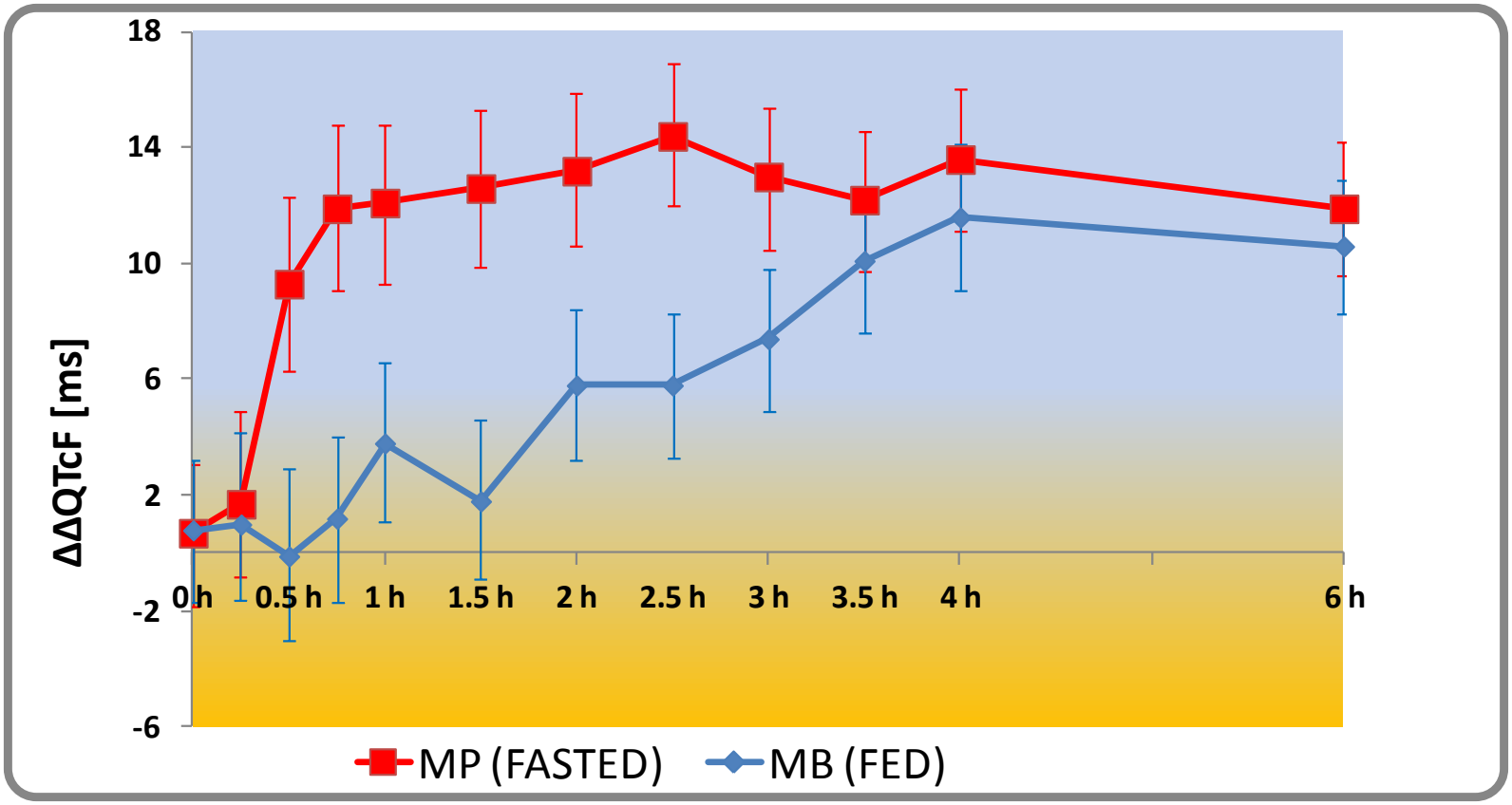
Ethnicity	Age (yrs)	Height (cm)	Weight (kg)
Caucasian	25.6 ± 4	172.8 ± 8.5	65 ± 7.2
Japanese	27.6 ± 3.3	167.1 ± 7.1	57.9 ± 5.6

- Caucasian *N*=13 (7♂, 6♀)
- Japanese *N*=19 (11♂, 8♀)
- Total *N*=32 (18♂, 14♀)

ECG and Data Analysis

- ECG were analysed automatically using the latest SL-12 algorithm
- All beats from all leads were manually over-read by a cardiologist highly experienced in QT analysis (manual adjudication)
- Individual heart rate corrections were calculated (QTcI***p***, QTcI***i***)
- Intervals were extracted and QTcF calculated

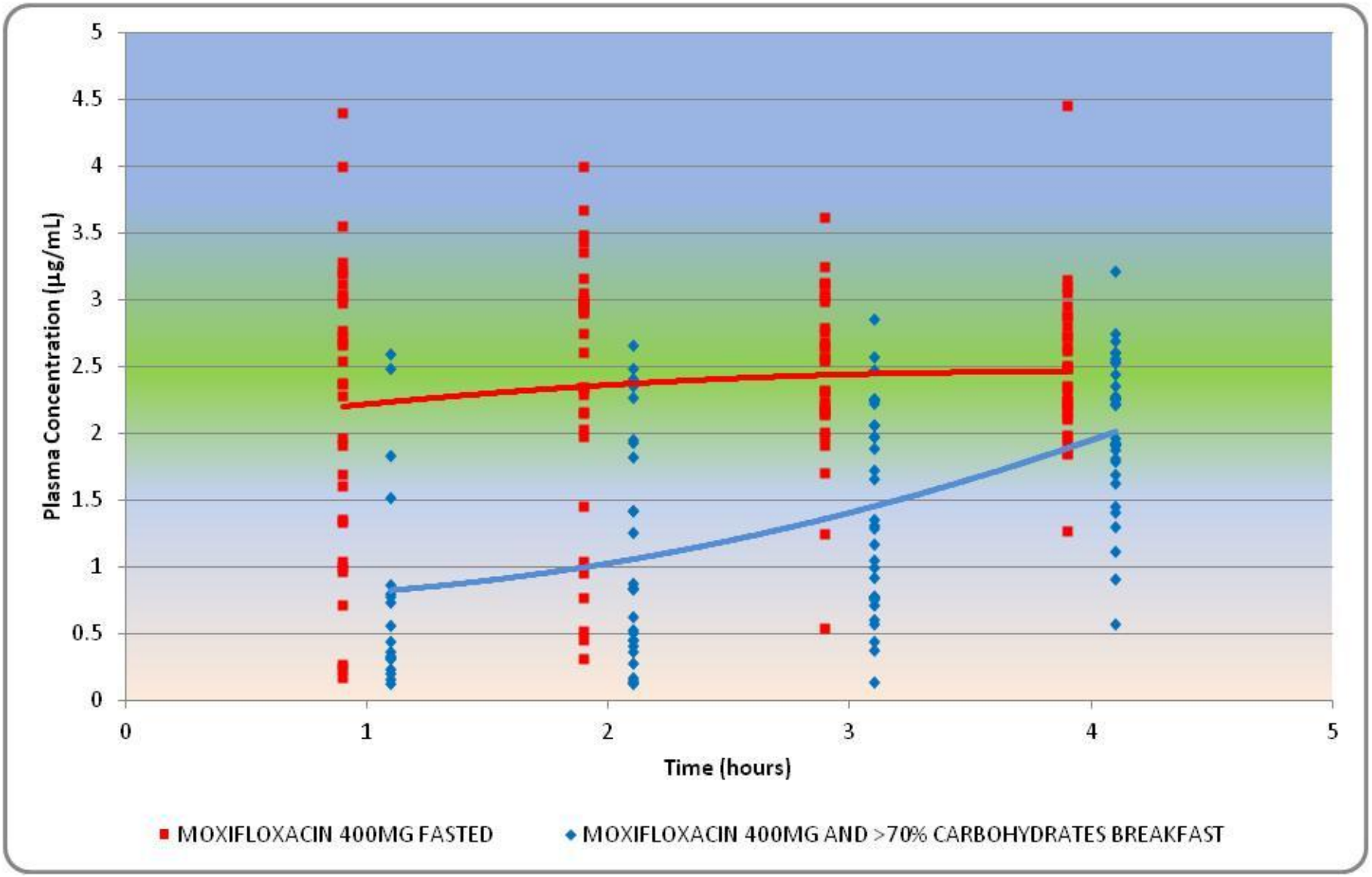
Effect of 400 mg Moxifloxacin on ΔΔQTcF in fed and fasted state



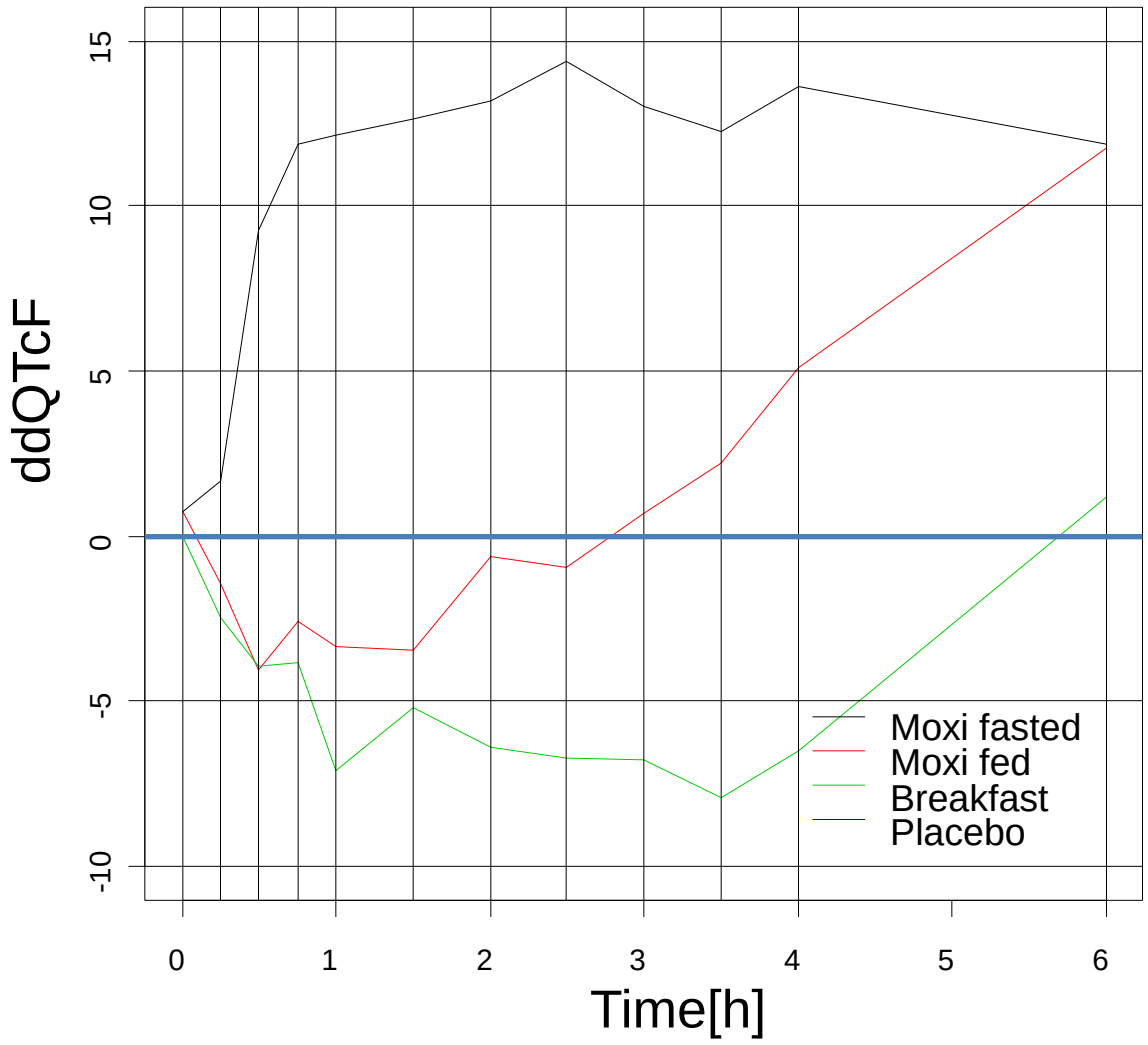
The maximum changes in QTcF was observed

in the fasted state at 2.5 hrs (14.4 ms) 4 hrs in the fed state (11.6 ms).

Moxifloxacin plasma concentration by administration: after fast and following a carbohydrate rich breakfast

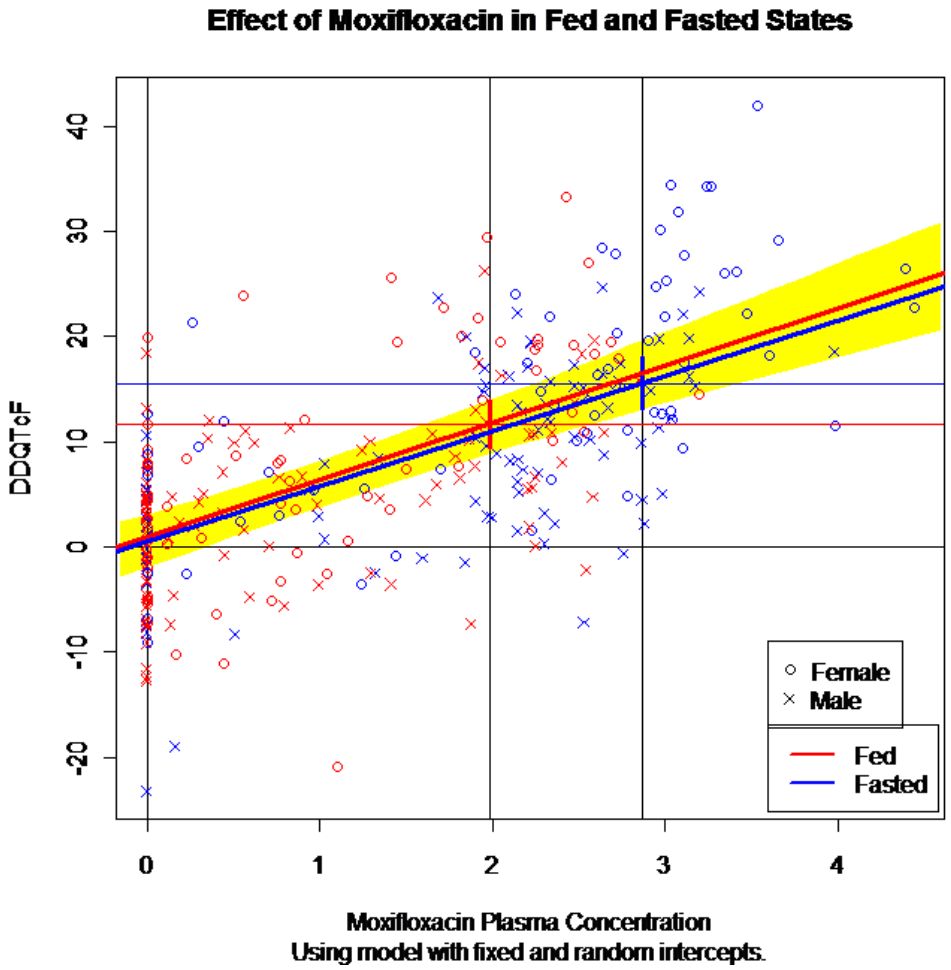


Differences to time matched placebo and PK-predicted effects



The observed effect of moxi in fasted state is the difference between the black and the blue curve. The model predicts the mean effect over time. The effect of moxifloxacin in the fed state is the difference between the green and the red lines: moxi with breakfast – breakfast alone.

The difference in the individual Cmax for the fed and fasted states has a kinetic origin



This figure displays the difference to time matched placebo of the change from average baseline of QTcF by moxifloxacin plasma concentration for the response in the fed & fasted arms.

The individual values are coded by sex (plot symbol) and race (colour). The regression lines are derived from a linear mixed effects model with concentration as covariate, race and sex and their interactions with concentration as fixed effects and random intercept and slope by subject. The vertical lines give the 95% confidence intervals for the predicted effect at the geometric mean C_{max} in the fed and fasted states respectively. The difference in predicted maximum effect of is essentially due to the different kinetics in the two conditions

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Summary

- The “typical moxi profile” is altered by food
  - This ought to be considered when setting sampling time points
- The effect is purely driven by a reduction and delay in absorption after a meal
  - The data in this study does not suggest that there is an electrophysiological effect beyond the pk reductions

Acknowledgements

- Dr Georg Ferber
- Dr Ulrike Lorch
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- Professor John Camm

Thank you

I do not think much of a man who is not wiser today than he was yesterday