SEX DIFFERENCES ON THE EFFECT OF MOXIFLOXACIN—A META-ANALYSIS OF FIVE THOROUGH QT STUDIES

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Introduction

Females can be more sensitive to the QTc prolonging effects of a drug compared to males. Sex differences in QT interval measurement are well documented1. At the same concentrations, females have been shown to have greater changes from baseline QTc for quinidine2 and ibutilide3 compared to males. Not only are the QT and QTc intervals longer in females than in males, but also the QT/RR relationship has been shown to be sex-specific4.

Recently a pooled analysis across 20 studies submitted to the FDA has shown that this difference extends to the QTc interval itself, with females having greater QTc prolongations (by about 1 msec) than women. This dose effect was shown by three separate published studies, and observed that the effects on QTcF increase with dose4. This dose response relationship may well be the reason for the greater effect of moxifloxacin on QTcF in females observed in this analysis and in literature5.

Discussion and Conclusion

The effect on the QTcF interval of a single 400 mg oral dose of moxifloxacin observed in the 5 studies conducted at our centre conforms well with published data6,7,8,9. The maximum effect was seen between 2 and 4 hours post-dose and lasted beyond the last observation time point 24 hours post dose. The effect on QTcF was found to be relatively similar across the 5 studies owing to the fact that they were conducted in the same clinic under very similar conditions and using the same equipment. The ECG data was analysed in our core laboratory at St George’s University using the same ECG adjudication process throughout.

For each of the studies a full 24 hour baseline was used with ECGs measured at the same time points as the endpoint day. In studies 1 to 4, study medication was given in a fasted state, while in study 5, it was given after a standardised American breakfast. Concentration effect model

Table 1: Number of subjects in each study

Study  Female  Male  Total
Study 1  39  41  80
Study 2  29  34  63
Study 3  14  34  48
Study 4  18  25  43
Study 5  25  25  50
Total  125  159  284

The predicted QTcF effects at a common moxifloxacin plasma concentration and the difference in slope between sexes. The predicted effects at a common concentrations are well documented1. At the same time points common to all studies were used for this analysis i.e. Pre-dose, 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 12:00 and 24:00 hours after dosing. In order to provide a valid ECG for a time point (three replicates), Fridericia-correted QTc (QTcF) was calculated and the mean over the replicates was used for each of the ECG parameters of interest.

Effect of moxifloxacin 400 mg on QTcF

For this analysis ‘double difference’ was used:

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Concentration effect model

A linear mixed effects model was used, with the placebo corrected change from average baseline as dependent variable and the corresponding plasma concentration of moxifloxacin as covariate. Further factors were study and sex and their interactions with concentration. The Akaike Information Criterion (AIC) was used to select the best fitting model.

Results

Table 1: Number of subjects in each study

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<thead>
<tr>
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Effect of moxifloxacin 400 mg on QTcF

Mean QTcF was increased following administration of 400 mg moxifloxacin compared to placebo. The greatest effect was observed at 3 hours post-dose (Figure 1). The overall moxifloxacin findings are in agreement with published literature6,7,8,9.

Mean change in QTcF (90% CI):

11.2 [9.7, 12.7] msec (females)
10.1 [8.8, 11.4] msec (males)

References

3. The pooled analysis reported by Florian et al. (2011) included 1,000 subjects from 20 studies, whereas this analysis only contained 284 subjects from five studies. However, the studies used in this analysis are much more homogenous than the sample used by Florian et al (2011), thus conclusively excluding a larger effect on QTcF. This would indicate that both sexes are equally sensitive to the 3R channel blocking properties of fluoroquinolone antibiotics.

Aims

To investigate whether pharmacodynamic or pharmacokinetic differences play a role to explain the apparent sex differences observed in various published thorough QT studies.

Methods

Studies

This meta-analysis is based on 5 thorough QT studies which have been performed at the same study site and are compliant with International Conference on Harmonization (ICH) E14 guideline. Each of these 5 studies were crossover-studies, placebo and active controlled, with a single dose of 400 mg moxifloxacin as active control. For the analysis presented here, the placebo and the moxifloxacin arm of each of the studies were compared to men.

In total, 284 subjects were included, of which 125 were female. A detailed split of this number by sex and study is given in Table 1.

In terms of moxifloxacin plasma concentrations, a clear difference between the sexes was observed. This can most likely be explained by the differences in body weight. Tomone et al (2011) reported that the effects on QTcF increase with dose. This dose response relationship may well be the reason for the greater effect of moxifloxacin on QTcF in females observed in this analysis and in literature5.

For each of the studies a full 24 hour baseline was used with ECGs measured at the same time points as the endpoint day. In studies 1 to 4, study medication was given in a fasted state, while in study 5, it was given after a standardised American breakfast. The pooled analysis reported by Florian et al. (2011) included 1,000 subjects from 20 studies, whereas this analysis only contained 284 subjects from five studies. However, the studies used in this analysis are much more homogenous than the sample used by Florian et al (2011), thus conclusively excluding a larger effect on QTcF. This would indicate that both sexes are equally sensitive to the 3R channel blocking properties of fluoroquinolone antibiotics.

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