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LETTER TO THE EDITOR

Time of the Day and Magnitude of the Effect of a Drug on the QTc Interval

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To the Editor

To accurately assess a drug's effect on QTc interval it is essential to identify the different sources of bias that may affect the extent of QTc prolongation of a drug. With this in mind, Kervezee *et al.*[1] recently published an article describing the effect of dosing time on levofloxacin-induced QTc prolongation.

The estimated concentration–QT relationship in the morning is concordant with the data previously published.[2] However, the apparently confounding results reported at different times are probably a consequence of the noninclusion of a placebo arm to allow for valid treatment group comparison, which is also recognized as a limitation by Garnett and Johannesen.[3] One might expect a description of the collection of data used for the development of the baseline model and an explanation for determination of the number of harmonic terms used. We assume that the data obtained before drug administration have been used to this end. If this is true, the approach has two drawbacks. We understand that meals were timed in synchrony with the drug intake, so they are not uniform with respect to real time. Given that a standardized meal would be expected to induce a decrease in QTcF of 6–8 ms, as previously described,[4] a standardized setting to establish the baseline model should have been used for correction for potential 24-h variation in the baseline QT interval. In other words, the baseline used to estimate the drug effect may be biased. The other point is that, if our assumption is correct, the number of subjects available for estimation of the drug-free model is decreasing over time. If that is so, there will be heteroscedasticity over time, which, in theory, should have been taken into account when fitting the model. We agree that this may be of less concern.

Kervezee *et al.* describe a dependent IOV on the time of drug administration (figure 3b). Variation is still considerable after correction for a circadian effect, i.e., when the concentration–effect relationship includes 24-h estimates of slope, depending on the time of the ECG recording (figure 3d). Therefore, the IOV steadiness when the concentration–effect relationship is described by a cosine function with two harmonics with periods of 24 and 12 h (figure 3f) seems rather an artifact and should benefit from some discussion if a real effect.

As detailed by Garnett and Johannesen,[3] the effect of dosing time on levofloxacin-induced QTc prolongation ought to be supported by formulated hypothesis on why the differences reported should arise.

1. Kervezee, L. *et al.* Levofloxacin-induced QTc prolongation depends on the time of drug administration. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 466–474 (2016).
2. Sugiyama, A. *et al.* Comparison of the effects of levofloxacin on QT/QTc interval assessed in both healthy Japanese and Caucasian subjects. *Br. J. Clin. Pharmacol.* **73**, 455–459 (2012).
3. Garnett, C. & Johannesen, L. Commentary on: "Levofloxacin-Induced QTc Prolongation Depends on the Time of Drug Administration". *CPT Pharmacometrics Syst. Pharmacol.* **5**, 452–454 (2016).
4. Taubel, J., Wong, A.H., Naseem, A., Ferber, G. & Camm, A.J. Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies. *J. Clin. Pharmacol.* **52**, 1558–1565 (2012).

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