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LETTER TO THE EDITOR

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

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To the Editor

We thank Täubel *et al.*[1] for their feedback on our work[2] and we appreciate the chance to address their comments here.

First, the observation that many physiological processes are subject to 24-h variations formed the rationale for conducting this study. This includes fluctuations in serum potassium levels, autonomic tone, and sensitivity or expression of cardiac ion channel (separately or in combination). Based on these observations, we (and others[3,4]) hypothesized that the magnitude of drug-induced QTc prolongation may depend on the time of day.

Second, we would like to clarify several aspects of our study design. In our clinical trial, 12 subjects completed 6 separate study days each (exceptions are explained in our article). Drug administration at the study days occurred randomized either at 2:00, 6:00, 10:00, 14:00, 18:00, or 22:00, and the study days were separated by at least 1 week. Subjects fasted from 2 h prior to these timepoints until 6 h after these timepoints. Six h after drug administration, subject ate a standardized meal and 10 h after drug administration, subjects consumed a standardized snack. Drug-free measurements to construct the baseline model were taken just before drug administration at each study day, at which point the subjects had been fasting for 2 h. Hence, we would like to point out that baseline data were collected using a standardized setting and is not biased with regard to real time or food intake. Since baseline data were collected prior to each drug administration at every study day, the number of subjects available for estimation of the drug-free model does not decrease over time. Therefore, we think that the 24-h variation in the baseline QT interval is properly accounted for in our study. The sensitivity analysis depicted in **Supplemental Figure 4** of our article shows that the application of previously published baseline models to our data results in a similar shape of the 24-h variation in the concentration–QT relationship compared to the use of our own baseline data.

However, we agree with Täubel *et al.* that the lack of a placebo arm in our study limits the interpretation of our findings, as we also mentioned in the Discussion section of our article. As a result of the noninclusion of a placebo arm, we believe that our findings may be explained in two ways: 1) levofloxacin-induced QTc prolongation depends on the time of drug administration, and/or 2) the placebo effect depends on the time of drug administration. To distinguish between these two possibilities, and to reveal the underlying mechanisms, further investigation is warranted.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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