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Adequate Design of Pharmacokinetic-Pharmacodynamic Studies Will Help Optimize Tuberculosis Treatment for the Future

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We read with interest the paper by Requena-Méndez and colleagues, who aimed to evaluate plasma concentrations of isoniazid administered daily and twice weekly [1]. The sampling strategy to assess the area under the concentration-time curve (AUC) consisted of obtaining two plasma samples at 2 and 6 h (C2 and C6, respectively) after intake of the drugs. In addition, the maximum concentration of the drug in serum (C_{max}) was defined as the higher of either the C2 or the C6 concentration. They concluded that low isoniazid exposure (the AUC from 0 to 6 h) or a low C_{max} was not associated with poorer clinical outcomes.

The authors summarized several limitations of their study. It is most likely that the design of their pharmacokinetic study (i.e., C2 and C6 monitoring) explains why they failed to find such an association. They chose C2 and C6 monitoring because of logistical reasons. Although this approach has been used frequently in the past, this sampling strategy is suited neither for capturing the C_{max} nor for accurately predicting the AUC of isoniazid. Earlier, Prahl and colleagues showed that currently used target values for C2 are not predictive of treatment efficacy and need to be redefined [2]. Due to the large pharmacokinetic variability of isoniazid, the true C_{max} will be captured only by intensive pharmacokinetic sampling [3]. In addition, estimation of the isoniazid AUC using two samples (C2 and C6) does not qualify to be placed among the best-performing optimal sampling strategies for isoniazid [4]. Obtaining a full pharmacokinetic curve and using a validated limited sampling strategy are the only two strategies of accurately predicting the AUC. A more practical approach would include a third sample at 4 h after drug intake [4]. To overcome practical complications like sample stability, dried blood spot monitoring can be helpful [5].

Requena-Mendez et al. suggested that weight-based twice-weekly dosing is still a suitable alternative. We argue that their study was not designed and lacked the power to relate this strategy to treatment outcome. Conclusions on treatment outcome may be further complicated by the fact that data regarding drug susceptibility were not available [1, 6]. The earlier meta-analysis on this subject showed that microbiological failure was more frequent with the intermittent dosing schedules [7]. Indeed, intermittent dosing should no longer be recommended [8].

Only a well-designed sampling schedule and information on drug intake and drug susceptibility in combination with long-term follow-up will provide relevant data that may help to optimize tuberculosis (TB) treatment.

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