Reply to “Adequate Design of Pharmacokinetic-Pharmacodynamic Studies Will Help Optimize Tuberculosis Treatment for the Future”

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We thank Sturkenboom et al. (1) for their interest in our study and their comments. The pragmatic study design based on two sampling points, 2 and 6 h after drug intake, reflected the real-world approach taken in this study, sampling patients attending a government clinic rather than in the controlled setting of a pharmacokinetic study suite. This sampling strategy has frequently been used in the past (2), and there are data to suggest that the peak serum concentration ($C_{\max}$) occurs between 1 and 2 h postdose when isoniazid is given on an empty stomach (3, 4). If only isoniazid is being measured, a two-sample strategy with estimation of 1- and 4-h concentrations may effectively capture both the $C_{\max}$ and the majority of delayed absorption (5). However, isoniazid is usually administered with other drugs which are somewhat more slowly absorbed (e.g., rifampin). In such cases, a 2- and 6-h-postdose sampling strategy facilitating study of both agents seems reasonable (5). In our study, the objective was to determine the pharmacokinetics of isoniazid and also rifampin, and thus the C2-C6 sampling strategy was chosen. Although a more intensive pharmacokinetic sampling would better capture the true $C_{\max}$ values (6), as suggested by the authors, the logistical demands of this approach would have compromised study recruitment in most of our community clinic field sites, rendering the study unfeasible.

We agree that it is likely that our data underestimates the true $C_{\max}$ and AUC, though there is no reason to believe that values would differ between groups. However, one factor that may delay the time at which $C_{\max}$ occurs ($T_{\max}$) is to take the drug with food, in particular with high-fat meals (5). Thus, it is recommended that isoniazid be given on an empty stomach. In our study, we were unable to adequately control or reliably measure the concomitant food intake of all the patients, and this fact may have influenced the final results. In this regard, another study is being undertaken with an aim to reliably control food intake with the drugs of patients, and at the same time, the pharmacokinetics of TB drugs will be measured at three time points: 2, 4, and 6 h after the drug intake. Larger studies like this one are required; using sparse population pharmacokinetic sampling schemes in different settings would be desirable, though these probably require a greater level of research infrastructure than is currently available in public clinics in Lima, Peru.

Regarding treatment outcome, in this subanalysis, we included only 41 drug-susceptible patients and excluded patients diagnosed with multidrug-resistant TB, patients who either abandoned treatment or did not properly complete treatment, and others who lacked a microbiologically confirmed diagnosis. However, we agree that our study was not designed to relate the treatment schedule strategy to treatment outcome and that larger studies with long-term follow-up are required to provide relevant data in this respect.

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