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References

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Reply to Gadkowski and Stout
To the Editor—Gadkowski and Stout [1] comment that the area under the curve between 0 and 6 h (AUC_{0–6h}) cannot serve as a surrogate for total exposure (AUC_{0–24h}) to rifampicin and that the results of our study [2] could be explained by delayed absorption of rifampicin in patients with tuberculosis (TB) who have type 2 diabetes (DM). We recently recorded full pharmacokinetic curves of rifampicin in 48 Indonesian patients with TB (unpublished data). Only 2 of 48 patients had a time to maximum concentration (T_{max}) of >4 h. The AUC_{0–4h} based on sampling at 0, 2, 4, and 6 h appeared to be an excellent surrogate for AUC_{0–24h} (Pearson correlation coefficient, 0.923; P < .001). Of course, this only applies in the absence of delayed absorption. In our study patients who had TB, with or without DM [2], the median T_{max} for rifampicin was 4 h in patients with TB and DM, compared with 2 h among those with TB alone. Individual T_{max} values show why this difference was not significant (P = .52) and certainly do not point to delayed absorption (table 1).

Gadkowski and Stout [1] also suggest that slightly different relative decreases in average rifampicin plasma concentrations between 4 and 6 h after administration of the dose indicate ongoing absorption in patients with TB and DM. As a rough approximation, we calculated rate constants on the basis of rifampicin concentrations at 4 and 6 h in all participants and used these to estimate AUC_{0–24h} values (linear/log trapezoidal rule). The geometric mean ratio for AUC_{0–24h} (patients with TB and DM versus those with TB alone) is 0.57, similar to the results we obtained based on the AUC_{0–6h}.

Gadkowski and Stout [1] also state that we did not match for sex and weight. However, we did match for sex, as mentioned in our publication. Matching for weight was not feasible, because patients with (type 2) DM generally have higher body weights. Therefore, in the multivariate analysis, we chose to assess the contributions of DM and body weight to the pharmacokinetics of rifampicin. As a rule of thumb, 15 subjects are required for every predictor in multiple linear regression [3]. Because our linear regression equation contained 2 predictors, the study group comprised 34 subjects, and all assumptions were met, linear regression was applicable. We agree that other linear models may also be valid to extrapolate the association between weight and area under the curve to those weight ranges in which data were available (i.e., low weights in patients with TB and DM and high weights in patients with TB alone). Considering the amount of data, no model can be preferred above the other. Of note, AUC_{0–6h} in subjects who weighed >50 kg was much lower in patients with both TB and DM than in those with TB alone (geometric mean ratio, 0.63), contrary to the statement made by Gadkowski and Stout [1]. Finally, the strong inverse association between fasting blood glucose level and rifampicin AUC_{0–6h} clearly confirms the importance of DM as an independent predictor beside body weight.

We conclude that our results are valid and remain tantalizing. Indonesian patients with TB and DM have lower plasma concentrations of rifampicin, which can be ascribed to differences in weight and diabetes or hyperglycemia. Follow-up studies to confirm these findings are underway.

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Potential conflicts of interest. All authors: no conflicts.

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Table 1. Distribution of time to maximum concentration (T_{max}) values between patients with tuberculosis (TB) and patients with TB and diabetes mellitus (DM).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>T_{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TB</td>
<td>2 4 6</td>
</tr>
<tr>
<td>Patients with TB and DM</td>
<td>7 9 1</td>
</tr>
<tr>
<td>Patients with TB</td>
<td>9 8 0</td>
</tr>
</tbody>
</table>

Antirheumatic Drugs and the Risk of Tuberculosis
To the Editor—In their recent study, Brassard et al. [1] measured the incidence rate of Mycobacterium tuberculosis disease (TB) among patients with rheumatoid arthritis and assessed whether use of disease-modifying antirheumatic drugs is associated with TB risk. The authors identified cases of TB on the basis of a single administrative claim that listed 1 of several