founder [5]. We controlled for the significant differences between groups by adjusting for the correspondents’ variables in the multivariable analysis and treating the confounding through purposeful selection method [3].

If we consider hospitalization for pneumonia, the adjusted hazard ratio (HR) decreased when the 2 covariates history of hospitalization for pneumonia and number of outpatient visits were added into the model. The adjusted HR was 0.81 (95% CI, 0.66–1.00; P = .060) without these variables and 0.74 (95% CI, 0.59–0.92; P = .007) when both variables were included in the final model. These 2 variables were statistically significant. The maximum change in the coefficients for any other variable remaining in the model was <11%. In this model, influenza vaccination was not a confounder. When the influenza vaccine status was added, the associations were essentially unchanged (pneumococcal vaccine HR, 0.76; 95% CI, 0.60–0.97; P = .026). The maximum change in all coefficients was <12%.

As can be seen in table 4 of our article [4], the effectiveness of pneumococcal polysaccharide vaccine for reducing hospitalization for pneumonia during influenza seasons was significant (HR, 0.69; 95% CI, 0.49–0.97; P = .031). This table only indicates the adjusting covariates in the initial models, but does not indicate the covariates in the final models. With regard to hospitalization for pneumonia during the influenza period, influenza vaccination status was neither statistically significant nor an important confounder.

In summary, we have estimated the effect of pneumococcal polysaccharide vaccine in parsimonious and robust models that adjusted for all covariates considered in previous studies. However, as commented on in the discussion, “as with all observational studies, the possible influence of residual confounding can not be completely excluded” [5, p.863].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References


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Pharmacokinetics of Rifampicin

TO THE EDITOR—Nijland et al. [1] present interesting data regarding the pharmacokinetics of rifampicin in patients with tuberculosis and diabetes mellitus. However, their conclusions are weakened by 2 important flaws in the study design. First, they used the area under the curve between 0 and 6 h (AUC0–6 h) as a surrogate for total rifampicin exposure. Time points beyond 6 h are routinely used to examine rifampicin pharmacokinetics, because the maximum concentration may occur as late as 8 h after administration of the dose [2]. The data presented in table 2 and figure 1 of the article strongly suggest delayed rifampicin absorption in the diabetic subjects, compared with the nondiabetic subjects. The median time to the maximum concentration was 4 h (the upper limit of the range was 6 h) in the diabetic subjects, compared with 2 h (upper limit of range, 4 h) in nondiabetic subjects; even though this difference was not statistically significant, it appears to have been a significant confounder. Furthermore, the relative decrease in rifampicin plasma concentrations between 4 and 6 h was ~47% in the nondiabetic subjects versus ~30% in the diabetic subjects, suggesting ongoing absorption in at least some subjects during this time. Examination of the plasma rifampicin concentrations at a later point would have greatly enhanced confidence that the difference in rifampicin pharmacokinetics between diabetic and nondiabetic patients with tuberculosis was an effect of malabsorption, as opposed to delayed absorption.

Second, the authors did not match the diabetic and nondiabetic subjects by weight and sex, which have both been associated with significant differences in rifampicin exposure [2]. Linear regression is inadequate to adjust for the difference in weights among the diabetic and nondiabetic subjects, particularly given the small sample size. As can be seen in figure 2 of Nijland et al. [1], 11 of the 17 nondiabetic subjects weighed <50 kg (compared with 4 of 17 diabetic subjects), and there is a cluster of 8 nondiabetic subjects who weighed <50 kg and who had very high rifampicin AUC0–6 h values, suggesting a nonlinear relationship between subject weight and rifampicin exposure at higher doses (in mg/kg). The area under the curve for nondiabetic subjects who weighed ≥50 kg falls well within the range for diabetic subjects in this study.

In short, the data presented by Nijland et al. [1] are tantalizing, but because of serious limitations, do not clearly demonstrate that type 2 diabetes is associated with decreased exposure to rifampicin.

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Angel Vila-Corcoles,1 Olga Ochoa-Gondar,1 and Teresa Rodriguez2
1Primary Care Service of Tarragona-Valis, Catalan Health Institute, Tarragona, and 2Department of Statistic and Research of Institut d’Investigació Atenció Primària Jordi Gol i Gurina, Barcelona, Spain

Reprints or correspondence: Dr. Angel Vila-Corcoles, Primary Care Service of Tarragona-Valis, Catalan Health Institute, Prat de la Riba, 39, 43001 Tarragona, Spain (avila.te妃.ics@gen.cat).

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

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tmax, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TB</td>
<td>2</td>
</tr>
<tr>
<td>and DM</td>
<td></td>
</tr>
<tr>
<td>Patients with TB and DM</td>
<td>7</td>
</tr>
<tr>
<td>Patients with TB</td>
<td>9</td>
</tr>
<tr>
<td>and DM</td>
<td>8</td>
</tr>
<tr>
<td>Patients with TB</td>
<td>9</td>
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<tr>
<td>Patients with TB</td>
<td>9</td>
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<td>and DM</td>
<td>8</td>
</tr>
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</table>

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 rifampin concentrations at 4 and 6 h in all participants and used these to estimate AUC0–24 h values (linear/log trapezoidal rule). The geometric mean ratio for AUC0–24 h (patients with TB and DM versus those with TB alone) is 0.57, similar to the results we obtained based on the AUC0–6 h.

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 few 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, AUC0–6 h 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 rifampin AUC0–6 h 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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Hanneke M. J. Nijland,1 R. E. Aarnoutse,2 R. Ruslami,3 and Reinout van Crevel2

Departments of1Clinical Pharmacy and 2Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and3Department of Pharmacology, Medical Faculty, Padjadjaran University, Bandung, Indonesia

References


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...