MAJOR ARTICLE

Exposure to Rifampicin Is Strongly Reduced in Patients with Tuberculosis and Type 2 Diabetes

Hanneke M. J. Nijland,[1] Rovina Ruslami,[4] Janneke E. Stalenhoef,[2] Erni J. Nelwan,[5] Bachti Alisjahbana,[3] Ron H. H. Nelwan,[5] Andre J. A. M. van der Ven,[2] Halim Danusantoso,[6] Rob E. Aarnoutse,[1] and Reinout van Crevel[2]

Departments of [1]Clinical Pharmacy and [2]Internal Medicine, Radboud University Nijmegen Medical Centre, The Netherlands; [3]Department of Internal Medicine, Hasan Sadikin Hospital, and [4]Department of Pharmacology, Medical Faculty, University of Padjadjaran, Bandung, and [5]Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, University of Indonesia, and [6]Indonesian Tuberculosis Control Association, Jakarta Branch, Jakarta, Indonesia

Background. Type 2 diabetes (DM) is a strong risk factor for tuberculosis (TB) and is associated with a slower response to TB treatment and a higher mortality rate. Because lower concentrations of anti-TB drugs may be a contributing factor, we compared the pharmacokinetics of rifampicin in patients with TB, with and without DM.

Methods. Seventeen adult Indonesian patients with TB and DM and 17 age- and sex-matched patients with TB and without DM were included in the study during the continuation phase of TB treatment. All patients received 450 mg of rifampicin (10 mg/kg) and 600 mg of isoniazid 3 times weekly. Steady-state plasma concentrations of rifampicin and its metabolite desacetylrifampicin were assessed at 0, 2, 4, and 6 h after drug intake.

Results. Geometric means of rifampicin exposure ($AUC_{0-6\ h}$) were 12.3 mg × h/L (95% confidence interval [CI], 8.0–24.2) in patients with TB and DM, and 25.9 mg × h/L (95% CI, 21.4–40.2) in patients with TB only ($P = .003$). Similar differences were found for the maximum concentration of rifampicin. No significant differences in time to maximum concentration of rifampicin were observed. The $AUC_{0-6\ h}$ of desacetylrifampicin was also much lower in patients with TB and DM versus patients with TB only (geometric mean, 0.60 vs. 3.2 mg × h/L; $P = .001$). Linear regression analysis revealed that higher body weight ($P < .001$), the presence of DM ($P = .06$), and plasma glucose concentration ($P = .016$) were correlated with exposure to rifampicin.

Conclusion. Exposure ($AUC_{0-6\ h}$) to rifampicin was 53% lower in Indonesian patients with TB and DM, compared with patients with TB only. Patients with TB and DM who have a higher body weight may need a higher dose of rifampicin.

Worldwide, the prevalence of type 2 diabetes (DM) is increasing—especially in developing countries, where tuberculosis (TB) is highly endemic. More specifically, it is estimated that, in 20 years, 75% of the patients with DM will live in countries that harbor the majority of cases of TB [1]. As a result, a growing number of patients with TB will have DM. Recent studies from Saudi Arabia [2], Russia [3], and from our own group in Indonesia [4] reveal that 10%–30% of patients with TB may have DM at this time. This is important, because DM seems to be associated with a less favorable response to TB treatment [5, 6]. Indeed, in a large Indonesian cohort of patients with TB, the presence of DM was associated with significantly lower sputum conversion rates after 8 weeks of treatment (B Alisjahbana et al., unpublished data).

Altered pharmacokinetics of anti-TB drugs may explain the adverse effect of DM on the response to TB treatment. It has been shown that patients who have DM have lower plasma concentrations of certain drugs [7, 8]. If this also applies to anti-TB drugs, this might explain the slower response to TB treatment in patients with DM. Lower plasma concentrations of anti-TB drugs have been associated with clinical failure and acquired drug resistance [9–11]. For rifampicin, a key drug in TB treatment, available evidence suggests that its efficacy is dependent on exposure to the drug or to the maximum drug concentrations achieved [12].

Recent studies, including ours, have reported low plasma concentrations of anti-TB drugs in patients with TB [13–16], but thus far, no studies have systematically examined the pharmacokinetics of TB drugs in patients

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Reprints and correspondence: Dr. Reinout van Crevel, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands (R.vanCrevel@aig.umcn.nl).

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Table 1. Characteristics of patients with tuberculosis (TB) and of patients with TB and type 2 diabetes (TB-DM).

	TB-DM group	TB group	*P*
Male sex, *n/N* (%)	9/17 (53)	11/17 (65)	.49[a]
Age, years	50 (28–60)	48 (27–59)	.85
Weight, kg	55.6 (36.6–75.2)	46.2 (33.6–70.8)	.01
Male patients	55.6 (45–75.2)	50.0 (33.6–55.2)	.03
Female patients	55.4 (36.6–65.2)	40.4 (36.2–70.8)	.15
BMI	23.9 (16.5–27.7)	18.9 (13.8–33.0)	.007
Male patients	20.9 (16.5–26.6)	19.1 (13.8–21.0)	.015
Female patients	24.8 (18.8–27.7)	18.7 (15.6–33.0)	.19
Fasting blood glucose, mmol/L	9.3 (6.3–12.3)	5.2 (4.4–5.6)	<.001
HbA1c, %	9.85 (0–13)	5.6 (0–7)	.014
Rifampicin dose, mg/kg body weight	8.1 (6.0–12.3)	9.7 (6.4–13.4)	.008

NOTE. Data are median (range), unless otherwise indicated. *P* values were calculated using the independent *t* test, unless otherwise indicated. BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HbA1c, hemoglobin A1c; TB, patients with tuberculosis; TB-DM, patients with tuberculosis and type 2 diabetes.

[a] *P* value calculated using Pearson's χ^2 test.

with DM. Therefore, in the present study, we compared plasma concentrations of rifampicin in patients with TB with and without DM.

METHODS

Study design and recruitment of subjects. We conducted a prospective pharmacokinetic study in the urban outpatient TB clinic Perkumpulan Pemberantasan Tuberculosis Indonesia, in Jakarta, Indonesia. Within the context of a larger study that evaluated the effect of DM on the immune response in patients with TB, patients with TB who had DM were included, and age- and sex-matched patients with TB who did not have DM were selected as control subjects.

Diagnosis of TB was based on clinical symptoms and chest radiography examination and was confirmed by microscopic detection of acid-fast bacilli and culture positive for *Mycobacterium tuberculosis*. Treatment consisted of a standard regimen of daily rifampicin, isoniazid, pyrazinamid, and ethambutol for 2 months, as well as rifampicin and isoniazid 3 times weekly for another 4 months, according to the Indonesian National Tuberculosis Program. All patients were administered identical TB drugs from a national manufacturer. Isoniazid and rifampicin were formulated in separate tablets. Bioequivalence of the rifampicin tablets to an international reference standard was established previously [17]. All patients were included after at least 2 weeks of TB treatment in the continuation phase. The Indonesian National Tuberculosis Program recommends 450 mg of rifampicin (10 mg/kg, considering the lower average body weight of Indonesian people) and 600 mg of isoniazid 3 times a week during the continuation phase.

Capillary and venous blood glucose levels were measured in all patients before the start of TB treatment. Newly established DM was diagnosed according to World Health Organization criteria [18]—that is, a fasting blood glucose value of $\geqslant$7.0 mmol/L, a capillary blood glucose value of $\geqslant$6.1 mmol/L, or a random plasma glucose value of $\geqslant$11.1 mmol/L, measured at 2 different time points. A diagnosis of DM was also accepted if patients already had established DM and were receiving antidiabetic agents. At the time of blood sampling for measurement of rifampicin pharmacokinetics, DM was confirmed, because hyperglycemia may disappear during TB treatment [19]. This confirmation showed that capillary fasting blood glucose concentrations were $\geqslant$6.1 mmol/L in all patients, and the fasting blood glucose concentration from plasma was $\geqslant$7.0 mmol/L in all but 1 subject whose DM was very strictly controlled (table 1). In accordance with national guidelines, patients with TB and DM were treated with oral antidiabetic drugs after 2–4 weeks of TB treatment. Study subjects had to be at least 18 years of age and were not allowed to use any drug that is known to affect the pharmacokinetics of rifampicin. Patients were excluded if they were pregnant or lactating, if they had gastrointestinal tract problems (e.g., diarrhea or vomiting on the days before the pharmacokinetic assessment), if they were HIV positive, or if they had an elevated creatinine level (>1.25 times above the upper limit of normal) or alanine transaminase level (>2 times the upper limit of normal). The study protocol of the main DM-immune response study was approved by the local institutional review board. Written informed consent for the pharmacokinetic substudy was obtained from all subjects.

Pharmacokinetic assessment. From 11 P.M. on the day preceding the study day until 4 h after drug intake on the study day, patients refrained from the intake of any food or drugs other than the study medication. Considering that the patients did not consume any food, they also did not take any prescribed antidiabetic drugs during this period.

On the day of pharmacokinetic assessment, the patients were administered 450 mg of rifampicin and 600 mg of isoniazid with 230 mL of still water. Serial venous blood samples were collected just prior to and 2, 4, and 6 h after witnessed drug intake in a fasting state. Plasma was immediately separated from blood samples and frozen at −20°C and was transferred to storage at −80°C within 60 h until transport on dry ice to The Netherlands for bioanalysis. The stability of rifampicin and its metabolite desacetylrifampicin under these conditions has been validated previously.

Bioanalysis. Total rifampicin concentrations and the concentrations of its main metabolite, desacetylrifampicin, were analyzed using a validated high-performance liquid chromatography method with UV detection. Two hundred μL of ace-

Table 2. Pharmacokinetic parameters of rifampicin and desacetylrifampicin in 17 patients with tuberculosis and type 2 diabetes (TB-DM) and in 17 patients with TB only.

Parameter	TB-DM group	TB group	Ratio of TB-DM to TB	*P*
Rifampicin[a]				
AUC_{0-6h}, mg × h/L	12.3 (8.0–24.2)	25.9 (21.4–40.2)	0.47 (0.31–0.77)	.003[b]
C_{max}, mg/L	3.49 (2.4–6.3)	6.74 (5.6–10.1)	0.52 (0.34–0.80)	.004[b]
C_{max} >8 mg/L (%)	1/17 (5.9)	8/17 (47.0)	…	.007[c]
T_{max}, median h (range)	4 (2–6)	2 (2–4)	…	.52[d]
Desacetylrifampicin				
AUC_{0-6h}, mg × h/L	0.60 (0.76–2.06)	3.2 (2.7–6.0)	0.27 (0.17–0.62)	.001[b]
C_{max}, mg/L	0.24 (0.26–0.65)	0.87 (0.72–1.60)	0.40 (0.09–0.82)	.023[b]
T_{max}, median h (range)	4 (4–6)	4 (4–6)	…	.524[d]

NOTE. Data are geometric mean (95% CI), unless otherwise indicated. $AUC_{0-6\ h}$, area under the plasma concentration-time curve from time 0 until 6 h after dose administration; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); C_{max}, maximum observed plasma concentration; T_{max}, time to C_{max}.

[a] 450 mg (10 mg/kg) administered in the continuation phase of TB treatment.

[b] *P* value calculated using the independent *t* test on natural logarithm–transformed data.

[c] *P* value calculated using Pearson's χ^2 test.

[d] *P* value calculated using the Wilcoxon rank sum test.

tonitrile and 10 μL of ascorbic acid solution were added to 200 μL of plasma sample. The mixture was vortexed for 20 s and centrifuged for 5 min, at which time 400 μL of 10 mmol/L potassium dihydrogen phosphate was added. The mixture was then vortexed and centrifuged again. Two hundred μL of the clear supernatant was injected in the high-performance liquid chromatography apparatus. Chromatographic analysis was performed on an Omnispher 5 C18 column (250 × 4.6 mm; Varian) protected with a Chromguard RP guard column (10 × 3 mm; Varian). The mobile phase consisted of 10 mmol/L potassium dihydrogen phosphate (pH, 4.5) and acetonitrile (percent by volume, 62%:38%). The flow rate was set at 1 mL/min, and the wavelength for UV detection was 334 nm. Rifampicin and desacetylrifampicin retention times were 7.8 min and 3.6 min, respectively. The lower limits of quantitation for rifampicin and desacetylrifampicin were 0.28 mg/L and 0.15 mg/L, respectively. Accuracy was 99.8%, 100.4%, and 100.4% for the rifampicin standard concentrations of 2.9 mg/L, 9.5 mg/L, and 23.7 mg/L, respectively. The accuracy of the desacetylrifampicin standard concentrations of 0.09 mg/L, 2.25 mg/L, and 27.0 mg/L was 103.9%, 102.4%, and 102.6%, respectively. Intraday precision and between-day precision (coefficient of variation, %) ranged from 0.7% to 1.1% and from 0.1% to 0.6% for rifampicin, and from 0.9% to 2.9% and from 0.5% to 3.6% for desacetylrifampicin, respectively.

Pharmacokinetic analysis. Pharmacokinetic parameters of rifampicin and desacetylrifampicin were calculated using noncompartmental methods. The area under the plasma concentration time curve from time 0 h until 6 hours after the dose ($AUC_{0-6\ h}$) was assessed using the linear trapezoidal rule. The highest observed plasma concentration was defined as C_{max}, and the corresponding sampling time was defined as T_{max}. C_{max} and T_{max} were determined directly from the plasma concentration-time data. Pharmacokinetic parameters were calculated using the WinNonlin software package, version 4.1 (Pharsight Corporation). The relative exposure of the metabolite desacetylrifampicin versus rifampicin was expressed as the ratio of the metabolite and the parent drug.

Data and statistical analysis. Differences in $AUC_{0-6\ h}$ and C_{max} values in patients with TB versus patients with TB and DM were tested with an independent sample *t* test on the natural logarithm–transformed pharmacokinetic data. Pearson's χ^2 test was used to determine the difference in proportions of patients reaching a reference peak plasma concentration of 8 mg/L for rifampicin [20, 21]. Values for T_{max} were not transformed and were compared using the Wilcoxon rank sum test. Univariate analyses were performed for the separate groups (patients with TB and patients with TB and DM) to assess the effect of sex, age, body weight, and fasting plasma glucose level. A multivariate linear regression analysis with forced entry was performed to assess the variation in rifampicin pharmacokinetics ($AUC_{0-6\ h}$ and C_{max}) attributable to the presence of DM and other variables that emerged from the univariate analyses. All statistical evaluations were performed with SPSS for Windows, version 12.0.1 (SPSS). *P* values <.05 were considered to be statistically significant in all analyses.

RESULTS

Patients. Thirty-six patients with pulmonary TB were recruited for the study, of whom 2 were excluded from further analysis. Rifampicin concentrations in 1 patient could not be analyzed because of interference from endogenous substances. Analysis of the second excluded patient revealed a trough

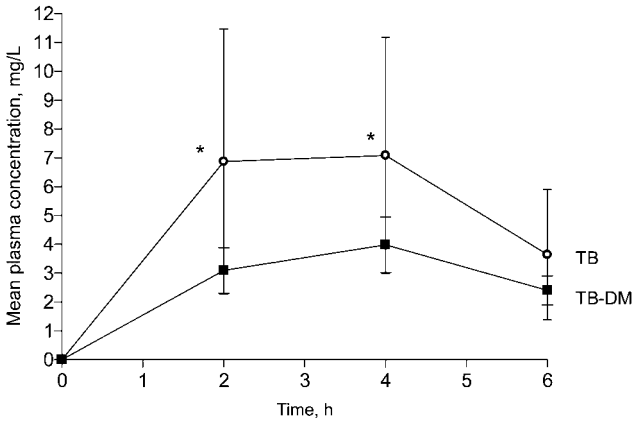

Figure 1. Mean plasma concentration (mg/L) over time (h) of rifampicin in 17 patients with tuberculosis (TB; *open circles)* and 17 patients with TB and with type 2 diabetes (DM; *closed squares),* with standard deviations. *P* value of comparison between groups <.05.

plasma rifampicin concentration of 2.8 mg/L before witnessed drug intake, which suggests that the patient had already taken the drug before arrival at the clinic. The remaining 34 patients presented with a 2–6-month history of cough (100% of patients), shortness of breath (85%), fever (91%), night sweats (68%), and weight loss (85%). All patients had chest radiograph abnormalities, and the results of sputum microscopy and culture for *M. tuberculosis* were positive for all patients. Characteristics of these patients are presented in table 1. Twelve (71%) of 17 patients with TB and DM used an oral antidiabetic treatment at the time of plasma rifampicin measurement. Glibenclamide was most commonly used; only 1 patient used glipizid. No patient was treated with metformin or insulin. Two patients used captopril for the treatment of hypertension. Concurrent use of glibenclamide, glipizide, or captopril is not known to affect the pharmacokinetics of anti-TB drugs. As expected, body weight and body mass index were significantly higher in the TB-DM group (table 1). As a result, the rifampicin dose per kilogram of body weight was lower for patients in the TB-DM group.

Pharmacokinetics of rifampicin and desacetylrifampicin. Marked interindividual variability was observed in exposure to rifampicin (range [$AUC_{0-6\,h}$], 5.5–71.6 mg × h/L). Patients with TB and DM had significantly lower rifampicin plasma concentrations than did patients with TB and without DM (table 2). The mean exposure to rifampicin ($AUC_{0-6\,h}$) in patients with TB and DM was 53% lower than the exposure in patients with TB only (figure 1). Similar differences were found for C_{max}, and a strong correlation was observed between $AUC_{0-6\,h}$ and C_{max} in both patients with TB only and patients with TB and DM (Pearson correlation coefficients, 0.983 and 0.987, respectively; $P < .01$). The percentage of patients who reached a reference value of at least 8 mg/L for rifampicin was significantly lower in patients with TB and DM compared with patients with TB only. Although median rifampicin T_{max} values differed between patients with TB and DM and patients with TB only, this difference did not reach statistical significance at all. With regard to desacetylrifampicin, the $AUC_{0-6\,h}$ and C_{max} values were significantly lower in the TB-DM group, whereas the T_{max} was not different. The geometric mean of the desacetylrifampicin/rifampicin $AUC_{0-6\,h}$ ratio was 0.13 (95% CI, 0.11–0.15) in the TB-only group, and 0.09 (95% CI, 0.06–0.11) in the TB-DM group ($P = .009$).

Univariate analyses. In the TB-DM group, no statistically significant difference was found in exposure between male and female patients ($AUC_{0-6\,h}$, 18.8 vs. 13.0 mg × h/L; not significant). In the TB-only group, male patients had lower rifampicin exposure than female patients (mean $AUC_{0-6\,h}$, 24.4 vs. 42.5 mg × h/L; $P = .048$). Age did not display a significant correlation with rifampicin pharmacokinetics. Body weight inversely correlated with rifampicin exposure, both in the TB-DM group (Pearson correlation coefficient, −0.462; $P = .062$) and in the TB-only group (Pearson correlation coefficient, −0.468; $P = .058$) (figure 2). The parallel lines in figure 2 demonstrate an equal effect of body weight on exposure in both groups. In addition, the difference between the dashed (TB) and solid (TB-DM) lines illustrates a clear effect of the presence of DM on the exposure to rifampicin. Fasting plasma glucose showed an inverse correlation with $AUC_{0-6\,h}$ (Pearson correlation coefficient, −0.476; $P = .004$) in the group as a whole.

Multivariate analysis. The assumptions for multivariate

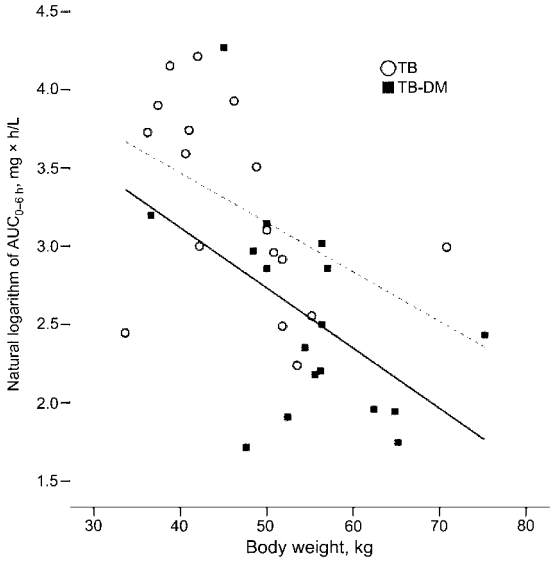

Figure 2. Natural logarithm of the area under the curve ($AUC_{0-6\,h}$) of rifampicin versus body weight (kg) for patients with tuberculosis (TB; *dashed line)* and for patients with TB and with type 2 diabetes (DM; *solid line).*

Table 3. Regression analysis of independent associations of various variables with exposure to rifampicin.

Model, regression parameter	B ± SE	*P*
1[a]		
Intercept	4.889 ± 0.544	<.001
Body weight	−0.035 ± 0.011	.004
DM	−0.425 ± 0.219	.062
2[b]		
Intercept	5.423 ± 0.517	<.001
Body weight	−0.034 ± 0.011	.004
Fasting plasma glucose at PK assessment	−0.114 ± 0.045	.016

NOTE. Exposure to rifampicin expressed as the area under the plasma concentration time curve from time 0 h until 6 h after the dose ($AUC_{0-6\ h}$). Adjusted R^2 is the effect size (i.e., 42.2% of the variation in the natural logarithm of $AUC_{0-6\ h}$) as explained by the model. B, the regression coefficient for determining the regression equation; DM, type 2 diabetes; PK, pharmacokinetic; SE, standard error.

[a] Adjusted $R^2 = 0.424$.

[b] Adjusted $R^2 = 0.466$.

linear regression were met, including the absence of multicollinearity, the independence of the outcome value, and the linearity of the model. The effect of the independent variables "body weight" and "DM" on the dependent variable "the natural logarithm of AUC_{0-6h}" were assessed in Model 1 (table 3). The absolute difference in the natural logarithm of $AUC_{0-6\ h}$ between patients with TB only and patients with TB and DM was 0.745. Every additional kilogram of body weight decreased the natural logarithm of $AUC_{0-6\ h}$ by 0.035. The weight difference between patients with TB only and patients with TB and DM was approximately 9.5 kg. The weight-corrected portion in the absolute difference for the presence of DM was 0.425, corresponding with 57% of the difference in exposure to rifampicin between groups.

A second regression analysis was performed in which fasting blood glucose level was assessed as an independent variable for the natural logarithm of $AUC_{0-6\ h}$. The presence of DM and fasting blood glucose level cannot be assessed simultaneously in 1 model, because these variables are highly correlated. Multivariate regression analysis revealed that fasting blood glucose level was significantly associated with rifampicin AUC_{0-6h} (table 3) and C_{max} (data not shown). Every extra millimole of fasting blood glucose per liter resulted in a decrease of the natural logarithm of $AUC_{0-6\ h}$ of 0.114. The mean difference of approximately 4 mmol/L in fasting plasma glucose between patients with TB only and patients with TB and DM corresponds with 61% of the difference in exposure to rifampicin. Fasting blood glucose and DM status show equal effects on the dependent variable natural logarithm of $AUC_{0-6\ h.}$ Thus, body weight and DM and hyperglycemia are strongly and inversely associated with rifampicin $AUC_{0-6\ h}$ and C_{max}.

DISCUSSION

In this study, we showed that exposure ($AUC_{0-6\ h}$) to rifampicin was 53% lower in Indonesian patients with TB and DM compared with patients with TB who did not have DM. Similarly, C_{max} of rifampicin was above the target concentration of 8 mg/L in only 1 (6%) of 17 patients with TB and DM compared with 8 (47%) of 17 patients with TB who did not have DM. A higher body weight and the presence of DM contributed to lower rifampicin exposure. In addition, more profound hyperglycemia was associated with lower plasma rifampicin concentrations.

The magnitude of the difference in $AUC_{0-6\ h}$ and C_{max} values of rifampicin between patients with TB and DM and patients with TB only was much larger than anticipated and is likely to be clinically relevant. A 50% lower exposure to a key TB drug such as rifampicin may cause clinical failures and may favor the emergence of drug resistance. In fact, the findings of this study suggest that the unfavorable response of patients with DM to anti-TB drugs [5, 6] may at least partially be explained by differences in pharmacokinetics. If these findings are confirmed, higher fixed dosages of rifampicin may be warranted for patients with DM and a higher body weight. If available, physicians may consider the assessment of plasma concentrations of rifampicin in patients with DM in order to individualize dosing. In this case, we would advise the use of multiple time point sampling.

Several mechanisms have been postulated to explain the altered pharmacokinetics of anti-TB drugs in patients with DM. The absorption, distribution, metabolism, and excretion of drugs could all be changed in patients with DM [8]. With regard to absorption, gastrointestinal tract problems are common in patients with DM. In this study, patients with diarrhea and vomiting were excluded from the study beforehand. Gastroparesis (delayed gastric emptying) could decrease the rate of drug absorption, as reflected in an increase in T_{max} and a decrease in rifampicin C_{max}. However, this study did not reveal any marked difference in T_{max} between the 2 study groups, which suggests that delayed absorption was not responsible for a lower C_{max} in patients with TB and DM. It should be acknowledged that the number of sampling points may have been too small to detect a change in T_{max}. Furthermore, it is unlikely that gastroparesis is associated with reduced absorption of rifampicin, because this drug is not subject to saturable first-pass metabolism after multiple doses and it does not have an absorption window in the gastrointestinal tract [22, 23].

The low exposure to rifampicin in patients with TB and DM may possibly be explained by the highly pH-dependent solubility and absorption of rifampicin [23, 24]. DM-associated hyperglycemia—which is strongly related to rifampicin exposure in this study—can reduce secretion of gastric hydrochloric acid (which results in a higher gastric pH) [7, 25], which, in

turn, has been associated with a decrease in rifampicin absorption [23]. This hypothesis needs confirmation, because gastric pH was not measured in our study, and other studies have not observed any effect of antacids on the pharmacokinetics of rifampicin [26].

With regard to metabolism and excretion, our results suggest that the metabolism of rifampicin to the metabolite desacetylrifampicin was reduced—or excretion of this metabolite was increased—in patients with TB and DM, at least in the first 6 h after drug administration. However, these findings do not explain the low exposure to rifampicin in patients with TB and DM; on the contrary, decreased metabolism of rifampicin in the hepatocytes of patients with DM might be explained by the expression of advanced glycosylation end-products in the liver [27], which impairs the normal function of basement membranes of cells, for example [28].

Linear regression analysis revealed an unexpectedly strong effect of body weight on the exposure to rifampicin. These results emphasize that rifampicin should be carefully dosed on the basis of body weight, as recommended by the World Health Organization and others [20]. Apparently, uniform dosing of rifampicin for all Indonesian patients ("one dose fits all") is inadequate. As was clearly shown, the fact that patients with TB and DM generally had higher body weights can only partially explain the differences in rifampicin pharmacokinetics.

This study was limited by the small sample size and by the limited number of time points for pharmacokinetic assessment. In addition, this study only assessed the pharmacokinetics of rifampicin in the continuation phase of treatment. Furthermore, this study focused on pharmacokinetics and did not assess the outcome of TB treatment.

In summary, we showed that exposure to rifampicin was strongly reduced in patients with TB and with DM. Patients with TB and concomitant DM and who have a higher body weight may possibly need a higher dose of rifampicin. Screening for DM at TB diagnosis could be worthwhile, and physicians may consider pharmacokinetic assessment of rifampicin in this patient group (if available). Additional studies are warranted to assess the influence of DM—as well as the possible benefit of active treatment of DM—on the pharmacokinetics of TB drugs and the outcome of TB treatment.

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Potential conflicts of interest. All authors: no conflicts.

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