PHARMACOKINETICS OF ANTI TUBERCULOSIS DRUGS
IN PULMONARY TUBERCULOSIS PATIENTS
WITH TYPE-2 DIABETES

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Word count: 3176
Abstract: 242
Number of tables: 3
Number of figures: 2
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Running title: Pharmacokinetics of TB drugs in diabetic TB patients
Keywords: Tuberculosis, diabetes, pharmacokinetics, Indonesia
ABSTRACT

Background

Altered pharmacokinetics of anti tuberculosis drugs may contribute to the increased risk of tuberculosis treatment failure in diabetic patients. We previously found that rifampicin exposure was two-fold lower in diabetic compared to non-diabetic tuberculosis-patients during the continuation phase of treatment. We now examined the influence of diabetes on pharmacokinetics of anti tuberculosis drugs in the intensive phase of tuberculosis treatment, and evaluated the effect of glycemic control.

Methods

Eighteen diabetic and 18 gender- and body weight- matched non-diabetic tuberculosis-patients were included in an Indonesian setting. Intensive pharmacokinetic sampling was performed for rifampicin, pyrazinamide and ethambutol at steady state. Rifampicin bioavailability was determined by comparing rifampicin exposure after oral and intravenous administration. Pharmacokinetic assessments were repeated in ten diabetic tuberculosis-patients after glycemic control.

Results

No differences in AUC\textsubscript{0-24h}, C\textsubscript{max}, T\textsubscript{max}, and half life of rifampicin, pyrazinamide and ethambutol were found between diabetic and non-diabetic tuberculosis-patients in the intensive phase of tuberculosis treatment. For rifampicin, oral bioavailability and metabolism were similar in diabetic and non-diabetic patients. Pharmacokinetic
parameters of anti tuberculosis drugs were not correlated with blood glucose level or glucose control.

Conclusion

Diabetes does not alter the pharmacokinetics of anti tuberculosis drugs during the intensive phase of tuberculosis treatment. Reduced exposure to rifampicin in diabetic patients in the continuation phase may be due to an increased body weight and possible differences in hepatic induction. Further research is needed to determine the cause of increased tuberculosis treatment failure in diabetic patients.
INTRODUCTION

Diabetes mellitus (DM) is a well-known risk factor for tuberculosis (TB) (1, 3, 7), with prevalence rates among TB patients ranging from 10 – 30% (1, 24, 25). There is a rapid increase in the global prevalence of DM, especially in the developing countries where TB is highly endemic. By the year of 2030, it is estimated that 80% of DM patients will live in the high-burden countries for TB (28). As a result, the number of TB patients with DM will further increase (18).

Diabetes exerts a negative effect on TB treatment, especially among patients with poor glycemic control, with more treatment failure and more relapse (2, 3, 7, 24). One of the possible underlying mechanisms could be altered pharmacokinetics of anti TB drugs. Lower plasma concentrations of TB drugs have been associated with clinical failure and acquired drug resistance (10, 23). Our previous study showed that the mean exposure (AUC_{0-6h}) to rifampicin as well the mean peak plasma concentration (C_{max}) of rifampicin were two-fold lower in Indonesian TB-patients with DM compared to those without DM (14). In multivariate analyses, a higher body weight (p<0.001), the presence of DM (p=0.06) and higher blood glucose levels (p=0.016) contributed to lower rifampicin plasma concentrations. These results suggested that heavier diabetic TB-patients may need to be treated with a higher dose of rifampicin, and that glycemic control may increase drug concentrations.

In our previous study TB-patients with and without DM were not matched for weight (6, 15), only rifampicin was measured, and limited sampling points were used to assess the pharmacokinetics of this drug. We have therefore performed an in-depth follow-up study, in which TB-patients with and without DM were matched for weight to be able to
disentangle the effects of DM and weight on plasma concentrations. Furthermore, rifampicin as well as pyrazinamide and ethambutol were studied and intensive pharmacokinetic sampling was performed. The first objective of the study was to compare the pharmacokinetics of rifampicin, pyrazinamide and ethambutol between weight-matched diabetic and non-diabetic TB patients. The second objective was to elaborate the possible mechanism of the alteration of pharmacokinetics of rifampicin, and the third was to evaluate the effect of glycemic control on the pharmacokinetics of TB drugs in diabetic TB-patients.

METHODS

Study Subjects

Diabetic TB-patients, who started with or were in the first two weeks of the intensive phase of TB treatment (arm 1) and non-diabetic TB-patients who were matched for gender and body weight (not more than 5 kg difference) as controls (arm 2) were recruited from an outpatient TB clinic in Bandung, Indonesia. The diagnosis of pulmonary TB was based on clinical symptoms, chest X-ray examination, sputum microscopy and *M. tuberculosis* culture. DM was diagnosed based on WHO criteria (31). In addition, patients were included if they had previously been diagnosed with DM and had poor glucose control at the time of recruitment, either with or without use of anti-diabetic drugs. Patients who were pregnant, below 18 or above 60 years of age, taking any drug that is known to affect the pharmacokinetics of TB drugs and those with diarrhea, vomiting or abnormal liver or kidney function were excluded. HIV status was assessed anonymously at the end of the study and patients with positive results were
excluded from further analysis because HIV infection may affect the pharmacokinetics of TB drugs.

**Study design**

A prospective, two-arm, three-period pharmacokinetic study was conducted. All study subjects received standard TB treatment consisting of rifampicin 450 mg (corresponding to 10 mg/kg in Indonesian patients, who have a low body weight), isoniazid 300 mg, pyrazinamide 1500 mg and ethambutol 750 mg daily for two months, followed by isoniazid 600 mg and rifampicin thrice weekly for four months, according to the Indonesian National Tuberculosis program. All patients received TB drugs from the same manufacturer, formulated in separate tablets. Bioequivalence of the rifampicin tablets and an international reference standard has been established before (26).

Adherence to TB drugs was monitored by pill-count and physician assessment methods (i.e. a physician assessing the patient if she/he forgot to take the drugs in previous two weeks) every time patients attended for follow-up (22).

A first pharmacokinetic (PK) assessment was performed two weeks after starting TB treatment, at steady-state (see figure 1). All TB drugs including rifampicin were given orally (study objective 1). A second PK assessment was performed the following day with the same dose of rifampicin administered intravenously, to enable an adequate discrimination between possible effects of DM on absorption, metabolism or elimination of rifampicin (study objective 2). For intravenous infusion, 450 mg rifampicin (Rifadin® - Bayer) was diluted in 250 ml of normal saline (NaCl 0.9%) and administered over a period of 90 min (rate of infusion: 5 mg/min) (8).
In accordance with national guidelines, TB-patients with DM were then treated with hypoglycaemic agents starting after 2-4 weeks of TB treatment. For ten selected patients, short-acting insulin (Humulin® 300 unit - Novo Nordisk) was used aiming at normal blood glucose levels within two to three weeks. Patients were educated about injecting insulin, recognizing hypoglycemia and monitoring of blood glucose at home. They were provided with a glucometer, and the study physician made dose adjustments if necessary. A third PK assessment was performed after normal blood glucose was achieved (see figure 1). In this PK assessment all TB drugs were given orally (study objective 3). After the third PK assessment, glucose control was continued with oral anti-diabetic drugs.

Based on the first objective and data from the previous study (20), it was calculated that a minimum number of 34 (17 in each arm) patients was required to be able to demonstrate a difference of at least 25% in the rifampicin exposure between diabetic and non-diabetic TB-patients by using the independent samples t-test with a significance level (α) of 5% and a power (1-β) of 80%. Informed consent was obtained from all subjects and the study was approved by the Independent Ethics Committee, Faculty of Medicine, University of Padjadjaran, Bandung, Indonesia.

**Pharmacokinetic assessment and bioanalysis**

Patients refrained from the intake of any food or drugs from 11 pm on the day preceding the PK 1 and 3 assessments until four hours after the intake of study medication. They took all TB drugs with 230ml of still water. Serial venous blood
samples were collected just prior to, and ½, 1, 1½, 2, 2½, 3, 4, 6, 8, and 12 hours after witnessed drug intake. Plasma was immediately separated and frozen at -20°C, transferred to -80°C within 72h and transported on dry ice to The Netherlands for bioanalysis. The stability of rifampicin, its metabolite desacetylrifampicin, pyrazinamide and ethambutol under all these conditions have been validated before. The plasma concentrations of rifampicin, desacetylrifampicin, pyrazinamide and ethambutol were assessed with validated high-performance liquid chromatographic (HPLC) assays with the methods as described before (21).

**Pharmacokinetic analysis**

A non-compartmental analysis with WinNonLin version 4.1 (Pharsight Corp., Mountain View, California) was performed to compute the pharmacokinetic parameters of rifampicin, desacetylrifampicin, pyrazinamide and ethambutol.

The maximum concentration of drug in plasma ($C_{\text{max}}$) and the time to this maximum concentration ($T_{\text{max}}$) were determined directly from the plasma concentration-time data. The terminal, log-linear period (log C versus t) was defined by the last data points ($N \geq 3$). The absolute value of the slope ($-\beta/2.303$, where $\beta$ is the first-order elimination rate constant) was calculated by least-squares linear regression analysis. Half life ($t_{1/2}$) was calculated from the expression $0.693/\beta$. If the concentration at 12h post dose ($C_{12}$) was quantifiable, the concentration at 24 h ($C_{24}$) was estimated using the equation $C_{24} = C_{12} \times e^{-\beta(t_{24}-t_{12})}$. The area under the concentration-time curve from 0 to 24h post dose (AUC$_0$-$24h$) was assessed using the linear-log trapezoidal rule from 0 up to the last
concentration. Apparent clearance (CL/F, where F is bioavailability) was calculated by dividing dose by AUC\textsubscript{0-24h}, and apparent volume of distribution (V/F) by dividing CL/F by β. The relative exposure of the metabolite desacetylrifampicin compared to rifampicin was expressed as the ratio of the metabolite and the parent drug. Oral bioavailability (F) of rifampicin was calculated by dividing the oral AUC\textsubscript{0-24h} (PK assessment 1) by the intravenous AUC\textsubscript{0-24h} (PK assessment 2).

**Statistical analysis**

Differences in AUC\textsubscript{0-24h}, C\textsubscript{max}, t\textsubscript{1/2}, CL/F and V/F in diabetic versus non-diabetic TB-patients (study objective 1) were tested with the independent-samples t-test, and a geometric mean ratio plus 95% confidence interval was calculated for every comparison. To be able to perform statistical testing using parametric tests, pharmacokinetic parameters that were not normally distributed were log-transformed, so the data become normally distributed. Values for T\textsubscript{max} were not transformed and were compared using Wilcoxon rank-sum test. Proportions of diabetic and non-diabetic patients with plasma concentrations of TB drugs above reference values were compared using the chi-square test. Reference plasma concentrations are defined as the usual drug concentrations found in patients as well as in healthy volunteers taking a standard dose of TB drugs; > 8 mg/L for rifampicin, > 20 mg/L for pyrazinamide and > 2 mg/L for ethambutol (18). The independent-samples t-test was used to examine the difference in oral bioavailability of rifampicin between diabetic versus non-diabetic TB-patients (study objective 2), while the paired t-test was used to assess the within-subject effect of glucose control on the pharmacokinetics of TB drugs (study objective 2).
3) and Wilcoxon signed-rank test was used to compare the $T_{\text{max}}$ values. All statistical evaluations were performed with SPSS for Windows, version 16.0.1 (SPSS Inc., Chicago, IL, USA). P values less than 0.05 were considered statistically significant in all analyses.

RESULTS

Patient’s baseline characteristics

Thirty six pulmonary TB patients were included in this study. Sixty percent of the diabetic-TB patients knew they had diabetes but no information on the date of diagnosis was recorded. The remaining 40% of diabetic-TB patients included in this study did not know that they had diabetes; diabetes was only diagnosed through screening. Patient characteristics were similar in the two arms, except for age; diabetic patients were older than non-diabetic patients (table 1). As patients were matched for body weight there was no difference in distribution of patients based on body weight, BMI or drug dose per kilogram between both arms. None of diabetic TB-patients used anti diabetic drugs at the time of the pharmacokinetic assessments. As would be expected diabetic patients had higher blood glucose values (table 1). None of the patients were HIV (+). Before and during all pharmacokinetic assessments, no patient had diarrhea or vomiting that might have affected the pharmacokinetic profiles that were recorded. No co-medication was recorded during the pharmacokinetic assessments.
Pharmacokinetics of TB drugs in diabetic and non-diabetic TB-patients

For comparison of pharmacokinetic parameters of TB drugs between diabetic and non-diabetic TB-patients (study objective 1), data were available for 17, 18 and 17 pairs of patients for rifampicin, pyrazinamide and ethambutol respectively. There were no difference in exposure to rifampicin, pyrazinamide nor ethambutol between diabetic and non-diabetic TB-patients (table 2, figure 2). Other pharmacokinetic parameters of these three drugs were similar between two groups (Table 2 and 3). An alternative test for analysis of the data, i.e. the paired t-test on the pharmacokinetic parameters of the pairs of matched patients, did not reveal a difference either. The proportion of patients reaching the reference values of rifampicin, pyrazinamide and ethambutol showed no significant differences between both arms (table 2 and 3). There were no significant correlations between rifampicin $AUC_{0-24h}$ (Pearson correlation coefficient -0.026, $p=0.884$) as well rifampicin $C_{max}$ (correlation coefficient 0.094, $p=0.598$) and fasting blood glucose levels, and the same applied for pyrazinamide and ethambutol. Age, which was higher in diabetic patients, did not display a significant correlation with rifampicin $AUC_{0-24h}$ and rifampicin $C_{max}$, nor with pharmacokinetics of pyrazinamide and ethambutol (data not shown). Male gender was associated with a lower rifampicin $AUC_{0-24h}$ ($p=0.037$) and $C_{max}$ ($p=0.057$), but this did not confound a possible relationship between DM and rifampicin exposure (data not shown). No association was found between gender and pharmacokinetics of pyrazinamide and ethambutol.
Absorption, metabolism and elimination of anti tuberculosis drugs

Comparison of pharmacokinetic assessments following oral and intravenous administration of rifampicin showed that oral bioavailability was similar in both groups (table 2). There was also no delayed absorption in diabetic TB-patients as shown by a similar T_{max} among diabetic and non-diabetic TB patients (table 2). Rifampicin clearance in both groups was also similar (table 2). Due to interferences in the plasma samples, desacetylrifampicin could not be measured accurately in all samples; nine data pairs were available for statistical analysis. The mean values for AUC_{0-24h} or C_{max} of desacetylrifampicin did not differ between two groups, but the numbers may be too small to find a significant difference. In addition, the desacetylrifampicin/rifampicin ratio for AUC_{0-24h} and C_{max} were similar in both groups (table 2). Like rifampicin, pyrazinamide and ethambutol showed no differences in absorption, metabolism and clearance between TB-patients with and without DM (table 3).

Effect of blood glucose control on pharmacokinetics of tuberculosis drugs

Ten patients received subcutaneous insulin to achieve and maintain normal blood glucose levels. After 5-6 weeks they had a decrease in fasting blood glucose levels (16.3 to 7.9 mmol/L, p=0.000) and HbA1c (10.6 to 7.1 %, p=0.001) and a significant (11%) weight gain. Repeated pharmacokinetic assessment did not show a significant increase in drug exposure. The ratio of AUC_{0-24h} after/before glycemic control was 1.15 for rifampicin, 0.94 for pyrazinamide and 0.87 for ethambutol (NS). None of the other pharmacokinetic parameters was significantly different after blood glucose control (data not shown).
DISCUSSION

This study showed that there were no differences in pharmacokinetics of rifampicin, pyrazinamide and ethambutol in the intensive phase of TB treatment between Indonesian TB-patients with and without DM who were matched for gender and body weight. Exposure to TB drugs as well their maximal concentration were not correlated with blood glucose level or glucose control, and oral bioavailability, absorption, metabolism and clearance of rifampicin, pyrazinamide and ethambutol were similar in both groups. This is an important information especially for highly active TB drugs like rifampicin and pyrazinamide. Ethambutol is a weak TB drug, the concentrations achieved with 15 mg per dosing barely produce serum concentration at or above the MIC.

The results of this study are different from our previous pharmacokinetic study of rifampicin in diabetic TB-patients (14). In that study we found that diabetic patients, especially those with poor glucose control, had a strongly reduced exposure to rifampicin. What factors can explain the contrasting results of the present and previous study? It is unlikely that the study setting plays a significant role. Patients in the present study came from a different clinic, but they have shown to be clinically, ethnically and genetically homogenous (12). The severity of DM is not an explanation either, as the fasting blood glucose level and HbA1c were higher in the present study (15.6 vs. 9.3 mmol/L and 11.2 vs. 9.85 % respectively). None of the diabetic patients in the current study versus 71% in the previous study took antidiabetic drugs before pharmacokinetic assessment (14), but there is no evidence that antidiabetic drugs affect the pharmacokinetics of antituberculous drugs (27).
The difference was also not due to more intensive sampling in the present study; limited time point analysis (AUC_{0-6h}) from the present data led to similar results (data not shown). The two studies used the drugs from the same manufacturer, and samples were processed, transferred and analyzed with the same validated methods. The pharmacokinetic data of TB drugs from non-diabetic TB-patients in this study were very similar to the data from patients (taking similar dose of rifampicin) in a previous study in the same setting (21). Therefore, from all the possible explanations we feel that only two may have had a significant role: matching for differences in body weight and timing of sampling (intensive versus continuation phase of TB-treatment).

Body weight is likely to have affected the results. In the previous study diabetic TB-patients had a 20% higher body weight than non-diabetic TB-patients, and a higher body weight results in a more than dose-proportional decrease in the mean AUC_{0-24h}, consistent with the non-linear pharmacokinetics of rifampicin (4, 17). Other studies have shown the effect of body weight (29, 30, 32). The higher body weight in diabetic patients in the previous study may have explained their lower rifampicin exposure, although regression analysis showed that DM and blood glucose level had an independent effect on plasma rifampicin exposure (14). To exclude possible confounding by body weight, in the present study we matched patients for body weight (and gender).

Timing of pharmacokinetic sampling may also have affected the results, because the current study was performed in the intensive phase and the previous study in the continuation phase of treatment, with rifampicin taken thrice weekly without pyrazinamide and ethambutol. Our studies in Indonesian patients have shown lower plasma rifampicin concentrations during the continuation phase (14, 16) than the
intensive phase of treatment (20, 21). On the one hand this seems counterintuitive because higher induction of liver cytochromes with daily use of rifampicin (4, 13) and co-administration of pyrazinamide (10) might lower rifampicin concentrations in the intensive phase. On the other hand, a higher body weight might decrease rifampicin concentrations during the continuation phase.

The current and previous studies suggest that DM does not alter the pharmacokinetics of TB drugs during the intensive phase of TB treatment, but possibly reduces rifampicin exposure during the continuation phase. This is supported by the fact that DM was strongly associated with positive sputum culture after continuation phase, but not after the intensive phase of TB treatment (2).

We hypothesize that the differential effect of DM on the pharmacokinetics of TB drugs during the intensive and continuation phase of treatment is due to differences in rifampicin induction. In the intensive phase, with daily administration of rifampicin, the activity of liver enzymes and transport pumps would be controlled completely by the very strong rifampicin induction (13). No drug or disease state would be able to overcome this. In contrast, thrice weekly dosing in the continuation phase may be associated with less induction on liver enzymes and transport mechanism, and the possible effect of DM might become manifest. In a study by Fromm et al (1996) on the induction of prehepatic and hepatic metabolism of verapamil by rifampicin, it was found that the half-life of enzyme induction is 1.5 – 2.1 days (5). Clearly this issue needs further investigation.

To summarize, we have examined the effect of DM on the pharmacokinetics of TB drugs in Indonesian diabetic TB-patients in the intensive phase of TB treatment. Our
data suggest that DM *per se* is not associated with altered pharmacokinetics of TB drugs in the intensive phase. It is likely that a higher body weight in diabetic TB-patients and especially in the continuation phase plays a role in the alteration of pharmacokinetics of TB drugs that might lead to a negative effect of TB treatment. Further study is needed to confirm these findings and to examine concentration-effect relationship (pharmacodynamics) of TB treatment. Also, more research is needed to examine why DM puts TB patients at risk for treatment failure, and if diabetic TB-patients should receive prolonged or dose-adjusted TB treatment.
ACKNOWLEDGEMENTS

We would like to thank the patients for their participation in this study. The staffs at the outpatient clinic Balai Besar Kesehatan Paru Masyarakat (BBKPM) and at Hasan Sadikin Hospital Bandung, in particular Lika Apriyani and Mutia Sesunan, are warmly thanked for their effort. The technicians of the Department of Clinical Pharmacy, Nijmegen, especially Alexander Kempers and Noor van Ewijk-Beneken Kolmer, are acknowledged for the analysis of the plasma samples. Thank you to Novo Nordisk Indonesia for the support in providing insulin injection and the glucometers. This study was supported by the Royal Academy of Arts and Sciences (KNAW) in The Netherlands, and by a grant from PRIOR, a research network supported by the Netherlands Foundation for Advancement of Tropical Research (NWO-WOTRO). R. Ruslami has a DC-fellowship from NWO-WOTRO (WB98-158). R. van Crevel has a fellowship from the Netherlands Organization for health research and development (ZonMw; 907-00-100).

Potential conflicts of interest.

All authors: no conflict.
REFERENCES


Table 1. Patient characteristics before start of treatment

<table>
<thead>
<tr>
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<th>TB–DM (n=18)</th>
<th>TB (n=18)</th>
<th>p value</th>
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<tr>
<td><strong>Gender Male</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>no. (%)</td>
<td>7 (39)</td>
<td>8 (44)</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>Age (year)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>47 (8)</td>
<td>35 (10)</td>
<td>0.00&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>Body weight (kg)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>47.3 (7.0)</td>
<td>47.3 (7.2)</td>
<td>0.85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>20.3 (3.5)</td>
<td>19.6 (3.0)</td>
<td>0.49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Drug dose&lt;sup&gt;c&lt;/sup&gt; (mg/kg BW)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rifampicin</td>
<td>9.7 (1.6)</td>
<td>9.6 (1.6)</td>
<td>0.82&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Ethambutol</td>
<td>16.2 (2.7)</td>
<td>16.1 (2.6)</td>
<td>0.86&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Pyrazinamide</td>
<td>32.5 (5.5)</td>
<td>32.2 (5.2)</td>
<td>0.86&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td><strong>Fasting Blood Glucose (mmol/L)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>16.6 (3.3)</td>
<td>5.6 (1.6)</td>
<td>0.00&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>HbA1c (%)</strong></td>
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<tr>
<td>Mean (SD)</td>
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<td><strong>Clinical manifestations (no., %)</strong></td>
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<tr>
<td>Cough</td>
<td>18 (100)</td>
<td>18 (100)</td>
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<tr>
<td>Hemoptysis</td>
<td>8 (44)</td>
<td>4 (22)</td>
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<tr>
<td>Shortness of breath</td>
<td>15 (83)</td>
<td>17 (94)</td>
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</tr>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
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<td>-----------------</td>
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<td></td>
</tr>
<tr>
<td>Fever</td>
<td>15 (83)</td>
<td>14 (79)</td>
<td></td>
</tr>
<tr>
<td>Loss weight</td>
<td>16 (89)</td>
<td>13 (72)</td>
<td></td>
</tr>
<tr>
<td>Sputum-smear (+)</td>
<td>16 (89)</td>
<td>18 (100)</td>
<td></td>
</tr>
<tr>
<td><em>M. tuberculosis</em> culture (+)</td>
<td>16 (89)</td>
<td>18 (100)</td>
<td></td>
</tr>
</tbody>
</table>

* a Pearson Chi-square
* b Independent t-test
* c data were presented as Mean (SD)
Table 2. Pharmacokinetic parameters of rifampicin and desacetylrifampicin in diabetic and non-diabetic tuberculosis patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TB-DM</th>
<th>TB</th>
<th>Ratio of TB-DM to TB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampicin</strong> (^\text{a}) (n=17) per group</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0-24\text{h}}) (mg·h/L)</td>
<td>49.0 [40.9 – 58.7]</td>
<td>50.6 [42.9 – 59.8]</td>
<td>0.97 [0.77 – 1.23]</td>
<td>0.81(^c)</td>
</tr>
<tr>
<td>C(_{\text{max}}) (mg/L)</td>
<td>10.5 [9.0 – 12.3]</td>
<td>9.6 [8.4 – 11.0]</td>
<td>1.09 [0.90 – 1.31]</td>
<td>0.81(^c)</td>
</tr>
<tr>
<td>C(_{\text{max}} &gt; 8\text{mg/L} ) (%)</td>
<td>15/16 (56.3)</td>
<td>8/16 (50%)</td>
<td>1.09 [0.90 – 1.31]</td>
<td>0.81(^c)</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h;median, range)</td>
<td>2 [0.5 – 4]</td>
<td>2.5 [1 – 4]</td>
<td>0.94 [0.78 – 1.12]</td>
<td>0.64(^c)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>2.1 [1.8 – 2.4]</td>
<td>2.2 [1.9 – 2.5]</td>
<td>0.94 [0.78 – 1.12]</td>
<td>0.64(^c)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>9.2 [7.7 – 11.0]</td>
<td>8.9 [7.5 – 10.5]</td>
<td>1.04 [0.83 – 1.31]</td>
<td>0.81(^c)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>27.4 [23.7 – 31.6]</td>
<td>27.6 [23.6 – 32.4]</td>
<td>0.98 [0.80 – 1.19]</td>
<td>0.81(^c)</td>
</tr>
<tr>
<td>F (%)</td>
<td>69</td>
<td>74</td>
<td>0.98 [0.80 – 1.19]</td>
<td>0.81(^c)</td>
</tr>
</tbody>
</table>

| **Desacetylrifampicin** \(^\text{b}\) \(n=9\) per group |             |             |                      |         |
| AUC\(_{0-24\text{h}}\) (mg·h/L) | 5.7 [3.9 – 8.4]  | 8.3 [5.6 – 12.1]  | 0.69 [0.42 – 1.15] | 0.14\(^c\) |
| C\(_{\text{max}}\) (mg/L)          | 1.1 [0.85 – 1.5] | 1.4 [1.1 – 2.0] | 0.78 [0.53 – 1.15] | 0.20\(^c\) |
| T\(_{\text{max}}\) (h;median, range) | 3.0 [2.0 – 4.0] | 4.0 [1.5 – 4.0] | 0.78 [0.53 – 1.15] | 0.20\(^c\) |
| t\(_{1/2}\) (h)                     | 2.3 [1.9 – 2.8] | 2.4 [2.1 – 2.8] | 0.94 [0.76 – 1.17] | 0.57\(^c\) |

| **Ratio desacetylrifampicin/rifampicin** |             |             |                      |         |
| AUC\(_{0-24\text{h}}\) | 0.11 [0.09 – 0.13] | 0.13 [0.10 – 0.17] | 0.83 [0.62 – 1.12] | 0.20\(^c\) |
| C\(_{\text{max}}\) | 0.12 [0.10 – 0.15] | 0.16 [0.12 – 0.19] | 0.80 [0.61 – 1.05] | 0.10\(^c\) |

Data were presented as geometric mean plus 95% Confidence Interval, unless stated otherwise.
AUC$_{0-24h}$: the area under the concentration-time curve of the drug in plasma from 0 to 24 h post-dose, $C_{\text{max}}$: the maximum concentration of drug in plasma, $T_{\text{max}}$: time to maximum concentration of drug in plasma, $t_{\frac{1}{2}}$: elimination half-life, CL/F: total clearance, V/F: apparent volume of distribution, F: bio-availability

b 450 mg (10 mg/kg) in the intensive phase of TB treatment

c Independent t-test on log transformed data

d Pearson Chi-square test

e Wilcoxon rank sum test
Table 3. Pharmacokinetic parameters of pyrazinamide and ethambutol in diabetic and non-diabetic tuberculosis patients

<table>
<thead>
<tr>
<th>Parameter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TB-DM</th>
<th>TB</th>
<th>Ratio of TB-DM to TB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pyrazinamide&lt;sup&gt;b&lt;/sup&gt; (n=18 per group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (mg·h/L)</td>
<td>409 [369 – 455]</td>
<td>468 [422 – 519]</td>
<td>0.88 [0.76 – 1.01]</td>
<td>0.07&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>45.5 [41.6 – 49.3]</td>
<td>47.0 [44.1 – 50.1]</td>
<td>0.96 [0.87 – 1.07]</td>
<td>0.47&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; &gt; 20mg/L (%)</td>
<td>18/18 (100)</td>
<td>18/18 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h; median, range)</td>
<td>1.0 (0.5 – 4.0)</td>
<td>1.5 [0.5 – 6.0]</td>
<td></td>
<td>0.61&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ethambutol&lt;sup&gt;e&lt;/sup&gt; (n=17 per group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (mg·h/L)</td>
<td>13.8 [12.0 – 15.9]</td>
<td>13.5 [12.0 – 15.1]</td>
<td>1.02 [0.86 – 1.22]</td>
<td>0.77&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>2.2 [1.8 – 2.7]</td>
<td>1.95 [1.6 – 2.4]</td>
<td>1.12 [0.86 – 1.47]</td>
<td>0.39&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; &gt; 2mg/L (%)</td>
<td>10/17 (58.8)</td>
<td>8/17 (47.1)</td>
<td></td>
<td>0.37&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h; median, range)</td>
<td>3(1.0 – 4.0)</td>
<td>3 (1.0 – 6.0)</td>
<td></td>
<td>0.93&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data were presented as geometric mean plus 95%Confidence Interval, unless stated otherwise.

<sup>a</sup>AUC<sub>0-24h</sub>: the area under the concentration-time curve of the drug in plasma from 0 to 24 h post-dose, C<sub>max</sub>: the maximum concentration of drug in plasma, T<sub>max</sub>: time to maximum concentration of drug in plasma

<sup>b</sup>1500 mg (30 mg/kg) in the intensive phase of TB treatment

<sup>c</sup>Independent t-test on log transformed data

<sup>d</sup>Wilcoxon rank sum test

<sup>e</sup>750 mg (15 mg/kg) in the intensive phase of TB treatment
† Pearson Chi-square test
Legend for figure 1

DM: diabetes mellitus, TB: tuberculosis. R: rifampicin 450 mg daily; Z: pyrazinamide 1500 mg daily; E: ethambutol 750 mg daily. p.o: per os; i.v: intravenous. PK: Pharmacokinetic assessment. PK I took place two weeks after starting TB treatment, all TB drugs were administered per os, PK II was performed the day after PK I, rifampicin 450 mg was administered intravenously by continuous infusion for 90 min. PK III was performed in 10 diabetic TB-patients 3 weeks after normal blood glucose level was achieved. Glycemic control was used insulin injection s.c (subcutaneous) with adjusted dose in order to normalize blood glucose within 2-3 weeks; all TB drugs were administered per os.
Legend for figure 2

Mean steady-state plasma concentration-time profiles of a) rifampicin (n=17), b) pyrazinamide (n=18) and c) ethambutol (n=17) in tuberculosis (TB) patients with (■) and without (○) diabetes (DM).
Figure 1. Study design

![Study design diagram]

- Blood Glucose control (Insulin s.c)
  - 2 weeks
  - 2-3 weeks
  - 3 weeks
- Normal Blood Glucose
  - PK I: R, Z, E (p.o)
  - PK II: R (iv)
  - PK III: R, Z, E (p.o)
- Start TB treatment
- DM
- Non-DM
Figure 2. Mean steady-state plasma concentration - time profiles of antituberculous drugs

(a) Mean plasma concentration of rifampicin (μg/mL)
(b) Mean plasma concentration of ethambutol (μg/mL)
(c) Mean plasma concentration of isoniazid (μg/mL)