Serum Levels of Antituberculosis Drugs and Their Effect on Tuberculosis Treatment Outcome

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Therapeutic drug monitoring in tuberculosis remains controversial. We evaluated the relationship between antituberculosis drug levels in blood and clinical outcome. Serum concentrations of first-line antituberculosis drugs were measured in tuberculosis patients between March 2006 and April 2013. Venous blood was drawn 2 h after drug ingestion and was analyzed using high-performance liquid chromatography-tandem mass spectrometry. We retrospectively reviewed the data and determined the association of serum drug levels with clinical outcome. Among 413 patients, the prevalences of low serum concentrations of isoniazid (INH), rifampin (RMP), ethambutol (EMB), and pyrazinamide (PZA) were 59.9%, 27.8%, 12.8%, and 8.7%, respectively. The low INH group had a greater percentage of patients with a history of tuberculosis treatment (19.2% versus 11.0%; P = 0.026) and was more likely to present with drug-resistant strains (17.6% versus 8.8%; P = 0.049) than the normal INH group; however, low levels of INH, RMP, EMB, and PZA were not related to treatment outcome. Low INH level had a tendency to be associated with 2-month culture positivity, but it was not statistically significant (P = 0.072) in multivariate analysis. Seventeen (4.1%) patients experienced a recurrence. However, the recurrence rate was not statistically different between the low and normal INH groups. Low serum INH may play a role in recurrence and in acquired drug resistance. However, the serum level of INH was not directly related to either treatment response or recurrence rate. The role and usefulness of therapeutic drug monitoring should be evaluated in further prospective studies.

Tuberculosis (TB) is a serious, persistent worldwide public health problem. Although most TB patients respond well to standard treatment, some patients show recurrence or exhibit acquired drug resistance (ADR). Low serum concentrations of anti-TB drugs may be associated with poor treatment outcome (1, 2); however, data linking drug levels to patient outcome are limited and inconclusive. Data obtained based on a preclinical model demonstrated that 1% of TB patients with perfect adherence would still develop multidrug-resistant (MDR) TB due to pharmacokinetic variability (3). In a recent meta-analysis, the pharmacokinetic variability of a single drug in the regimen was significantly associated with ADR and failure of therapy in TB patients (4). Because serum concentrations of anti-TB drugs are known to vary considerably between individuals (5–8), it is important to examine whether their concentrations can affect clinical outcomes in standard treatment settings. The aim of this study was to evaluate the prevalence of low drug levels and the clinical impact of the serum levels of anti-TB drugs during the treatment of TB.

MATERIALS AND METHODS

Study patients and data collection. Patients who were diagnosed with TB at Seoul National University Bundang Hospital in Korea and who had undergone consecutive measurements of anti-TB drug concentrations in blood were enrolled in the study. The study patients received daily anti-TB drugs for at least 1 week before the measurement of serum anti-TB drug levels. The anti-TB drugs were all single drug products rather than fixed-dose combinations; the prescribed doses were 300 to 400 mg of isoniazid (INH), 600 mg of rifampin (RMP), 800 mg of ethambutol (EMB), and 1,500 mg of pyrazinamide (PZA) for patients weighing >50 kg. In patients weighing <50 kg, the doses were reduced to 300 mg of INH, 450 mg of RMP, 600 mg of EMB, and 1,000 mg of PZA.

There has been concern regarding low INH levels in Korean patients treated for TB owing to the high proportion of rapid acetylators in Asian populations. We thus performed therapeutic drug monitoring (TDM) as a routine practice in our institution during the study period. Although the present study was not prospective, all of the participating physicians had similar clinical practice patterns and followed up with patients regularly with monthly chest radiography, sputum staining for acid-fast bacilli, mycobacterial culture, and laboratory tests (complete blood cell count; levels of albumin, cholesterol, and creatinine; and liver function tests). Age, sex, presence of underlying disease, laboratory findings, radiologic findings, and treatment outcomes were investigated. Treatment failure was defined as a positive sputum smear or culture at 5 months or later during treatment. A successful outcome was defined as “cure (negative sputum culture in the last month and on ≥1 previous occasion)” or “completed” (completed treatment but does not meet the criteria of cure or failure) (9). Patients were usually followed up for 2 years after the completion of treatment. Some patients were referred to another hospital for the treatment of TB. The National TB Registration System (http://is.cdc.go.kr/) was used to identify patients who had a recurrence after the completion of follow-up.

This study was approved by the Seoul National University Bundang Hospital Institutional Review Boards for Clinical Research (IRB no. B-1412/280-117), and requirement for informed consent was waived owing to the retrospective study design.

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There were a total of 413 patients included in the study. Drug ingestion to estimate peak concentrations of INH, RMP, EMB, and PZA was administered under fasting conditions. Serum levels were measured 2 h after drug ingestion. Data are presented as mean ± SD unless indicated otherwise. There were a total of 413 patients included in the study.

**Measurement of drug concentration.** The anti-TB drugs were administered under fasting conditions. Serum levels were measured 2 h after drug ingestion to estimate peak concentrations of INH, RMP, EMB, and PZA. Acetyl-INH, a metabolite of INH, was also measured. Serum was immediately frozen after centrifugation and was stored at −70°C until analysis. Drug levels were measured using the high-performance liquid chromatography-tandem mass spectrometry method as previously described (10). The therapeutic level of each drug was defined as 3 to 6 μg/ml for INH, 8 to 24 μg/ml for RMP, 2 to 6 μg/ml for EMB, and 20 to 50 μg/ml for PZA (1, 8).

**Statistical analysis.** Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA) and STATA 13.0 (StataCorp LP, TX, USA) software. Serum drug levels were dichotomized into normal or low if they were within or above the expected range or low if they were below the expected range. Variables were compared between patients with low and normal drug levels using the Student t test for continuous variables and a chi-square (χ²) test or Fisher’s exact test for categorical variables. Multivariable logistic regression analysis was performed to evaluate risk factors for low INH level and 2-month mycobacterial culture positivity. A two-sided P value of <0.05 was regarded as statistically significant. Classification and regression tree (CART) analysis was performed to evaluate the impact of baseline characteristics associated with INH resistance.

**Concentration of Anti-TB Drugs and Outcome**

TABLE 1 Baseline characteristics of the study patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. (%) of patients</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), yr</td>
<td>48 (17–92)</td>
<td></td>
</tr>
<tr>
<td>Sex, female</td>
<td>187 (45.3)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.8 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>209 (50.6)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>95 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>60 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>49 (11.5)</td>
<td></td>
</tr>
<tr>
<td>History of previous TB</td>
<td>65 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>58/385 (14.0)</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>33 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Initial sputum smear positivityb</td>
<td>92/364 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Drug susceptibility test</td>
<td>243 (58.8)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture proven</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>PCR confirmed</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Drug-resistant TB</td>
<td>36 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>9 (2.1)</td>
<td></td>
</tr>
</tbody>
</table>

a Data are presented as no. (%) or mean ± standard deviation (SD) unless indicated otherwise. There were a total of 413 patients included in the study.

b Evaluated in pulmonary TB.

**TABLE 2 Serum concentration of each tuberculosis drug**

<table>
<thead>
<tr>
<th>Tuberculosis</th>
<th>Drug level (μg/ml)</th>
<th>Therapeutic range (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>2.8 ± 1.4</td>
<td>2–6</td>
</tr>
<tr>
<td>RMP</td>
<td>10.2 ± 3.7</td>
<td>8–24</td>
</tr>
<tr>
<td>EMB</td>
<td>3.7 ± 0.9</td>
<td>2–6</td>
</tr>
<tr>
<td>PZA</td>
<td>36.1 ± 13.2</td>
<td>20–50</td>
</tr>
</tbody>
</table>

a Data are presented as mean ± SD.
drug level on the treatment outcomes using R statistical software (http://www.r-project.org/).

RESULTS
During the study period, drug levels were measured in 413 patients. The mean time from the start of treatment at which drug levels were measured was 31.4 ± 24.9 days. The median follow-up duration of the patients was 2.1 (0.1 to 9) years. The baseline characteristics of the patients are presented in Table 1. Female patients comprised 45.3% of the study subjects, 15.7% of patients had a history of TB treatment, and none of the patients had concomitant human immunodeficiency virus (HIV) infection. A drug susceptibility test was performed in 243 (58.8%) patients. The number of patients with drug-resistant TB (resistant to one of the following: INH, RMP, EMB, or PZA) was 36. Nine patients presented with initial MDR-TB. The mean serum levels of each drug are shown in Table 2. The prevalences of a low serum concentration of INH, RMP, EMB, and PZA were 245 out of 409 patients (59.9%), 115 out of 413 patients (27.8%), 53 out of 413 patients (12.8%), and 33 out of 378 patients (8.7%), respectively (Table 3 and Fig. 1). The number of patients who received PZA was the lowest since some of the patients stopped PZA because of adverse effects. Among the 245 patients with low INH levels, 69 (28.2%) had their INH dose adjusted (Table 3). However, repeated measurements of drug levels were performed in only one patient. This patient showed low INH levels even after an increase in the INH dose from 300 mg to 400 mg.

Previous history of TB treatment was more common in patients with low INH levels (low INH versus high INH, 19.2% versus 11.0%; P = 0.026). The low INH group had more drug-resistant strains (17.6% versus 8.8%; P = 0.049) than the normal INH group; however, low levels of RMP, EMB, and PZA were not related to a history of TB or drug-resistant TB. The signs of severe disease in chest radiograph were more frequent in the low INH group than those in the normal INH group (Table 3).

Two-month culture conversion rates, treatment outcomes, and recurrence rates were not significantly different between the low and normal drug level groups (Table 4). These results were not changed when the data were analyzed excluding patients with dosage adjustment (data not shown). Among 413 patients, 17 (4.1%) patients experienced a recurrence, and 13 out of 17 patients initially showed low levels of INH. After excluding patients with initial drug-resistant TB, 10 out of 14 patients who experienced recurrence showed low levels of INH. However, the recurrence rate was not significantly different between patients with low and normal INH levels (Table 4). Among the 14 patients who experienced recurrence, two presented with MDR-TB and two presented with
TABLE 5 Comparison of patients with low and normal isoniazid levels after excluding drug-resistant TB patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low (n = 219)</th>
<th>Normal (n = 156)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), yr</td>
<td>48 (18–88)</td>
<td>46 (17–91)</td>
<td>0.754</td>
</tr>
<tr>
<td>Sex, female</td>
<td>83 (37.9)</td>
<td>89 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.3 ± 3.1</td>
<td>20.2 ± 2.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35/194 (18.0)</td>
<td>21/138 (15.2)</td>
<td>0.498</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (13.7)</td>
<td>17 (10.9)</td>
<td>0.467</td>
</tr>
<tr>
<td>History of previous TB</td>
<td>36 (16.4)</td>
<td>16 (10.3)</td>
<td>0.088</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.0 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>0.454</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>168.0 ± 36.3</td>
<td>163.8 ± 34.5</td>
<td>0.268</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>92.1 ± 33.4</td>
<td>88.4 ± 28.6</td>
<td>0.269</td>
</tr>
<tr>
<td>Initial sputum smear positivity</td>
<td>51/206 (24.8)</td>
<td>30/149 (20.1)</td>
<td>0.306</td>
</tr>
<tr>
<td>Presence of cavity</td>
<td>59/215 (27.1)</td>
<td>31/148 (20.9)</td>
<td>0.159</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>17/214 (7.9)</td>
<td>7/148 (4.7)</td>
<td>0.227</td>
</tr>
<tr>
<td>Acetyl-INH/INH ratio</td>
<td>0.8 ± 0.6</td>
<td>0.3 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INH dosage (mg/kg)</td>
<td>5.6 ± 1.1</td>
<td>6.2 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fast acetylator</td>
<td>127/226 (58.4)</td>
<td>22/159 (13.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data are presented as no. (%) or mean ± SD unless otherwise indicated.

INH-resistant TB. An initial drug sensitivity test was performed on only one of these four patients. This patient was initially diagnosed with drug-sensitive TB, but after recurrence, the patient presented with INH-resistant TB. The other three patients with drug-resistant recurrence had been successfully treated with first-line drugs for their initial illness. It is unclear whether the recurrence in these three patients was caused by ADR, as initial drug sensitivity tests had not been performed in these three patients. Three of the four patients who presented with drug-resistant recurrence had low INH levels during their initial treatments.

Low INH levels were associated with male sex, high body mass index, high acetyl-INH/INH ratio, and low INH dose per kilogram of body weight (Table 5). Multivariate analysis also showed that male sex, high acetyl-INH/INH ratio, and low INH dose per kilogram of body weight were independent risk factors of low INH levels (Table 6).

When we compared patients with and without mycobacterial culture conversion within 2 months, old age, initial sputum smear positivity, the presence of cavity, bilateral lesions in chest radiograph, drug-resistant TB, and low serum concentration of INH were associated with 2-month mycobacterial culture positivity (Table 7). Low INH level had a tendency to be associated with 2-month culture positivity, but it was not statistically significant (P = 0.072) in multivariate logistic regression analysis (Table 8).

TABLE 6 Risk factors of low INH level after excluding drug-resistant tuberculosis patients (n = 375)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.99</td>
<td>0.97–1.00</td>
<td>0.290</td>
</tr>
<tr>
<td>Male</td>
<td>2.01</td>
<td>1.11–3.62</td>
<td>0.020</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.05</td>
<td>0.93–1.18</td>
<td>0.364</td>
</tr>
<tr>
<td>Acetyl-INH/INH ratio</td>
<td>35.08</td>
<td>13.55–90.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INH dosage (mg/kg)</td>
<td>0.7</td>
<td>0.50–0.97</td>
<td>0.036</td>
</tr>
</tbody>
</table>

TABLE 7 Comparison of patients with and without culture conversion within 2 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (n = 19)</th>
<th>Yes (n = 173)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), yr</td>
<td>66 (34–92)</td>
<td>51 (22–88)</td>
<td>0.041</td>
</tr>
<tr>
<td>Sex, female</td>
<td>4 (21.0)</td>
<td>74 (42.7)</td>
<td>0.067</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19.7 ± 2.6</td>
<td>20.7 ± 3.1</td>
<td>0.220</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2/17 (11.8)</td>
<td>26/154 (16.9)</td>
<td>0.588</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (31.6)</td>
<td>27 (15.6)</td>
<td>0.143</td>
</tr>
<tr>
<td>History of previous TB</td>
<td>7 (36.8)</td>
<td>34 (19.7)</td>
<td>0.083</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>0.051</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>156.2 ± 32.8</td>
<td>166.2 ± 35.3</td>
<td>0.241</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>94.5 ± 38.2</td>
<td>91.6 ± 34.2</td>
<td>0.735</td>
</tr>
<tr>
<td>Initial sputum smear positivity</td>
<td>13 (68.4)</td>
<td>56 (32.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of cavity</td>
<td>14 (73.7)</td>
<td>53 (30.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>5 (26.3)</td>
<td>11 (6.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Drug-resistant TB</td>
<td>7 (36.8)</td>
<td>18 (10.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>INH level (µg/ml)</td>
<td>2.2 ± 0.9</td>
<td>3.0 ± 1.5</td>
<td>0.030</td>
</tr>
<tr>
<td>RMP level (µg/ml)</td>
<td>9.5 ± 2.6</td>
<td>10.4 ± 3.7</td>
<td>0.309</td>
</tr>
<tr>
<td>EMB level (µg/ml)</td>
<td>4.3 ± 1.9</td>
<td>3.8 ± 1.8</td>
<td>0.243</td>
</tr>
<tr>
<td>PZA level (µg/ml)</td>
<td>36.9 ± 9.7</td>
<td>36.2 ± 12.1</td>
<td>0.821</td>
</tr>
</tbody>
</table>

*Data are presented as no. (%) or mean ± SD unless otherwise indicated.

DISCUSSION

In this study, about 60% of the patients showed low serum INH levels. A low serum level of INH was associated with a history of TB treatment and drug-resistant strains; however, the serum concentrations of RMP, EMB, and PZA were not related to these factors. Recurrence rates and other treatment outcomes did not differ between patients with low-level and normal-level anti-TB drugs. Patients with delayed culture conversion had a tendency toward lower INH levels than those without, but this trend was not statistically significant.

Although there have been several reports that showed low anti-TB drug levels in patients with TB (5–8), few studies have examined whether low drug concentrations affect patient response to TB treatment (11). Recently, several studies tried to evaluate the effect of anti-TB drug concentrations on treatment outcomes (3, 12–14). One study performed in the United States included 42 patients with slow responses to treatment. The study showed that 50% to 60% of the patients had low concentrations of INH and RMP (12). Another study, conducted in Canada, showed that serum levels of INH and RMP were low in 76.6% and 68.4% of the patients, respectively, and that five patients with ADR showed low levels of at least one drug (13). Because TDM was performed in small numbers of selected patients with comorbidities or slow treatment responses, these studies did not clearly demonstrate the effect of low drug levels on treatment outcomes.
In our study, we measured the serum concentrations of anti-TB drugs in large numbers of consecutive non-HIV TB patients in a clinical practice setting with the standard 4-drug combination therapy. Treatment outcomes and recurrence rates were thoroughly evaluated by using national TB registration data.

In the present study, most of the patients had drug-sensitive TB, and there were no HIV-positive patients. Therefore, treatment failure and death were rare. The reason the correlation between low INH level and poor treatment outcome was not statistically significant may have been the small number of recurrence and treatment failure cases. However, compared with patients with normal INH levels, a history of TB treatment and initial drug-resistant TB were more common among patients with low INH levels. This finding suggests that low INH levels may affect the risk of TB relapse, although it is uncertain whether patients with histories of TB had low serum INH levels at the time of the first TB treatment. Although the implication of this finding was not clear, it may represent indirect evidence suggesting that INH levels play a role in recurrence and acquired drug resistance.

Only one case in our cohort had a definitive diagnosis of ADR and showed low INH levels at initial treatment. We suspected ADR in three patients who suffered recurrence, but we could not prove it because of the absence of an initial drug susceptibility test. Thus, a long-term prospective study is required to confirm the association of pharmacokinetic variability and ADR.

We measured serum levels 2 h after drug ingestion (C_{2h}). It is known that the efficacy of first-line drugs is driven by the area under the curve (AUC) rather than by C_{2h} (15, 16). However, AUC monitoring is impossible in real clinical practice. Furthermore, previous studies showed that the C_{2h} values of INH, RMP, EMB, and PZA had been found to correlate well with the maximum concentration of drugs (C_{max}) (1). Limited-sampling strategies, using two to three samples to predict AUC values, may solve the problem of inadequate drug exposure assessment by C_{2h} monitoring (16).

It is well known that TB patients with HIV coinfection show more frequent low drug levels than those shown by non-HIV TB patients owing to malabsorption and drug interaction (17, 18). Few studies have evaluated drug levels in homogeneous non-HIV TB patients (7). Our data may be useful in clinical practice for TB treatment where frequency of coinfection with HIV is low.

The prevalence of low INH levels was about 60% and was higher than that of other anti-TB drugs. INH is metabolized by hepatic acetylation by N-acetyltransferase 2 (NAT2); the NAT2 gene has several alleles associated with rapid and slow acetylation, which are associated with 88% of all variability in INH systemic clearance (19). It is known that fast acetylators are more common in Asian than in Western populations (20). We defined fast acetylators as those with metabolic rates of >0.55 acetyl-INH/INH ratio (21); thus, 40.4% were defined as fast acetylators in our study. Using multivariate analysis, we found that male sex, high acetyl-INH and INH ratios that reflect rapid acetylation were the
most potent risk factors for low INH levels (adjusted odds ratio (OR), 35.08; 95% confidence interval, 13.55 to 90.80; P < 0.001). The high prevalence of low INH levels may thus result from the high prevalence of fast acetylaters (22).

In our study, RMP, EMB, and PZA levels were not related to TB treatment response. This finding differs from those of previous studies that showed that PZA levels were associated with treatment outcomes (17, 23). Using study populations that consist of different ethnicities or patients with positive HIV statuses may lead to different results. We performed CART analysis to evaluate the impact of drug level on treatment outcomes. The CART analysis using INH, RMP, EMB, and PZA levels to predict treatment outcomes is shown in Fig. 2. The best single predictor for treatment success was PZA level (≥20.7 μg/ml), but PZA level alone was not sufficient to predict the treatment outcome. In this model, agreement for the prediction of treatment success was 328/336 (97.6%), and agreement for the prediction of treatment failure was 13/36 (36.1%).

Considering the prediction of Srivastava et al. (3) that 1% of patients will develop ADR, TDM costs for 100 patients are lower than those of a single treatment course of MDR-TB in Korea (24). A cost-benefit analysis of TDM should be undertaken before recommending its widespread use in TB patients.

The present study has several limitations. It is a retrospective study and thus has the potential for selection bias. However, most of the drug levels were measured consecutively. The mean time of the measurement of drug levels from the start of treatment was 31.4 days. Among 413 patients, 351 (84.9%) underwent TDM within 30 days from the start of treatment irrespective of treatment response. Therefore, there is little chance of bias. Because dose adjustment of anti-TB drugs was performed individually by the clinicians rather than on the basis of a predefined protocol, the effect of TDM-directed therapy could not be evaluated. In 69 patients with low INH levels, the INH dose was changed, but subsequent measurement of drug levels was not performed. Therefore, it is difficult to draw any conclusions about the effect of INH concentrations on treatment outcomes. In addition, the NAT2 genotype was not checked, so the differences caused by the NAT2 genotype in this population could not be evaluated. Genotyping for the Mycobacterium tuberculosis strain was also not performed in patients who presented with recurrent TB; thus, we could not clearly distinguish between true relapse and reinfection.

In conclusion, low serum concentrations of INH were related to a history of TB treatment and to drug-resistant strains. Although the implication of this finding is unclear, it might represent indirect evidence that suggests that INH levels play a role in recurrence and in ADR. We did not find, however, that low INH level was directly related either to treatment response or to recurrence rate in this study. Due to the limitations of our study, we are not able to make recommendations on routine TDM for general TB patients. The role and usefulness of TDM should be evaluated in further prospective studies.

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