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DRUG DISCOVERY AND RESISTANCE

Effects of type 2 diabetes mellitus on the population pharmacokinetics of rifampin in tuberculosis patients

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SUMMARY

Diabetes mellitus (DM) is a well-known risk factor to develop tuberculosis (TB). Some reports indicate the serum concentrations of anti-TB drugs are lower in patients with TB and DM than those with TB only. Therefore, we developed a nonlinear mixed-effects model (NONMEM) to determine the population PK parameters of rifampin and assessed the effects of DM status in patients with TB. One-compartment linear modeling with first-order absorption was evaluated using the 206 plasma samples of rifampin from 54 patients with DM. Based on the final model, DM affected the absorption rate constant (ka) and the volume of distribution (Vd) of rifampin. The body mass index (BMI) of the patients affected rifampin clearance (CL). The ka of rifampin in patients with TB and DM was greater than that in patients with TB only. Further, the predicted Vd in patients with DM was greater than that in patients without DM. As Vd is inversely correlated with plasma concentrations, the rifampin concentrations were predicted to be lower in the patients with DM. The authors recommend administering the greater doses of rifampin for the treatment of TB in patients with DM compared with the doses for the patients without DM to prevent treatment failure.

1. Introduction

The incidence of and mortality from tuberculosis (TB) are in a decreasing trend worldwide. However, they are still remarkable. It is reported that the new cases of TB were approximately 8.6 million and the mortality from TB approximately 1.3 million annually in the world [1]. A number of risk factors such as HIV infection, diabetes mellitus (DM), and development of multidrug resistant-TB (MDR-TB) influence the prevalence and treatment outcomes of TB infection [1,2].

Many previous studies discovered that the incidence of DM in patients with TB was higher than that in control groups [3–8]. Even though the relationship between TB and DM was apparent in the early stage of studies, the clinical relevance of such observations was not clear [8]. However, in later studies, it was found that DM affected the effective concentrations of antituberculosis drugs [9–11]. Nijland et al. reported that the exposure to rifampin (the AUC_{0-6h}) was lower in patients with TB and DM than that in patients with TB without DM [9]. Moreover, a recent study showed that the blood concentrations of isoniazid and rifampin were lower in patients with TB and DM than those in patients with TB without DM [11].

Even though the conventional pharmacokinetics (PK) of antituberculosis agents have been studied extensively [9,10,12,13], the

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studies on the population PK of antituberculosis agents are few. Especially, no known results of the DM influence on the population PK parameters of rifampin had been revealed. Population PK is to measure the variability of the drug concentrations between individuals and widely used to adjust the dosage regimen [14]. Therefore, we developed a population PK modeling using a nonlinear mixed-effects model (NONMEM) to determine the population PK parameters of antituberculosis agents in patients with TB and to reveal the impact of the DM status on the PK and other factors affecting rifampin concentrations. We anticipate this approach be useful in adjusting rifampin doses in patients with TB in DM status.

2. Methods

2.1. Patient profile

This study was prospectively conducted in 54 patients with TB with ($n = 21$) or without DM ($n = 33$) who were admitted at Seoul National University Bundang Hospital in Seongnam, Korea. The study protocol was approved by the institutional review board (IRB) at the Hospital (IRB No. B-0711/051-008) and followed all tenets of Helsinki Declarations. All study participants were informed of the purpose of the research and the experimental details by providing and explaining the written informed consent. All enrolled patients were older than 19 years of age. Tuberculosis was diagnosed by clinical presentation, chest X-ray, and sputum smear and culture. The patients who have taken rifampin, isoniazid, pyrazinamide, and ethambutol (HREZ) for at least 1 week after diagnosis of TB were eligible to participate this study and admitted to the Hospital. In line with WHO recommendations, the initial TB treatment regimen was rifampin 10 mg/kg/d (up to 450 mg or 600 mg), isoniazid 5 mg/kg/d (up to 300 mg or 400 mg), pyrazinamide 15–30 mg/kg/d (up to 1500 mg), and ethambutol 15–20 mg/kg/d (up to 800 mg, 1000 mg or 1200 mg) [15–17]. The patients were diagnosed as DM when their fasting blood glucose levels were over 126 mg/dl or post-prandial glucose levels over 200 mg/dl. The patients were excluded when they were experiencing the adverse effects of antituberculosis agents such as abnormal liver or renal function tests or having conditions such as absorption disorders that possibly affect antituberculosis drug concentrations. Medications that potentially alter the PK of antituberculosis drugs were prohibited during the entire study period.

2.2. Experimental design

All enrolled patients fasted from 11 p.m. the day before blood sampling until antituberculosis drug administration. Isoniazid, rifampin, ethambutol, and pyrazinamide (HREZ) were administered orally, with tepid water, at 8 a.m on Day 1 of the study. Blood samples (5 ml each) were withdrawn at 1, 2, 4, and 6 h after antituberculosis drug administration. All blood samples were immediately placed in EDTA-containing tubes. Plasma was separated by centrifuging the sample at 16,100 g for 10 min at 4 °C and stored at −70 °C until the analysis of rifampin concentrations.

2.3. Rifampin assay

Rifampin concentrations in plasma were analyzed using a high performance liquid chromatographic method with mass spectrometric detection (LC/MS/MS) [18] with Hydrosphere C_{18} chromatographic column (column details: 3-μm bead diameter, 50 × 2.0-mm internal diameter; YMC Co., Kyoto, Japan). The mobile phase was running at a gradient of 0.3% (v/v) formic acid in methanol (Solvent A) with 0.3% formic acid in water (Solvent B) at a flow rate 400 μl/min.

2.4. Population PK analysis

A total of 206 rifampin plasma samples from 54 subjects were available to develop a NONMEM for the population PK of rifampin. The model was developed using the NONMEM software (version 7.20; ICON Development Solutions, Ellicott City, MD) running on GFortran. Model-building steps and associated data analysis were performed using Xpose (version 4.3.2; http://xpose.sourceforge.net/). The first-order conditional estimation method (FOCE) was used to develop modeling and guided by changes in the NONMEM objective function value (OFV). The minimum value of OFV was considered to be most fitted model and it was assumed that a one-compartment linear model featuring first-order absorption (the NONMEM subroutine ADVAN2 TRANS2) would be most appropriate. Estimations of typical population PK parameters, random inter-individual variabilities (IIV) of the parameters, and residual variabilities between predicted and observed values, were performed using the first-order conditional estimation method (FOCE) featuring IIV (η) and residual variance interaction (ε). IIV and residual variability were modeled as follows:

Interindividual variability (IIV): proportional and exponential relationship:

$$KA = TVKA \times (1 + \eta 1)$$

$$CL = TVV \times e^{\eta 2}$$

$$V = TVV \times e^{\eta 3}$$

Residual variability: combined additive and proportional relationship:

$$W = SQRT\left(\theta^2 + (IPRED \times \theta)^2\right)$$

$$C_{ij} = C_{predij} + W \times \varepsilon_1$$

In the equations above, TVCL indicates the typical value of clearance (CL), TVV the typical volume of distribution (Vd), and TVKA the typical value of the absorption rate constant (ka). Whereas ε_1 is the residual variability with a mean of zero and an estimated variance of σ^2, η_n is the random IIV of each pharmacokinetic parameter with a mean of zero and an estimated variance of ω^2. Unknown residual variability was estimated using a combination of additive and proportional error models.

Model selection was achieved using the objective function value (OFV) and was built via forward selection and backward elimination of covariates. During forward selection, a drop of >3.84 after addition of a single parameter was considered significant, corresponding to the 5% significance level with a single degree of freedom. In contrast, an increase of >6.63 during backward elimination of a single parameter from the full model was statistically significant ($p < 0.01$) at a single degree of freedom, and the parameter was thus retained.

2.5. Model evaluation

A visual predictive check was employed to identify the finally-selected PK model and predict observations therefrom. In addition, 1000 sets of data were generated by a bootstrap method [15], with replacement by original data. The finally-selected PK model was fitted to each bootstrap dataset. The median, and the 2.5th and

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