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Limited sampling strategies for determining the area under the plasma concentration–time curve for isoniazid might be a valuable approach for optimizing treatment in adult patients with tuberculosis

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ABSTRACT

This study aimed to develop clinically feasible models of limited sampling strategy (LSS) for estimation of the area under the concentration–time curve (AUC_{24h}) for isoniazid, that could be applied easily in daily clinical practice for dosage adjustment in adult patients with tuberculosis. Isoniazid plasma concentrations ($n = 1665$) from 185 adult tuberculous patients were used for the development and validation of LSS models to estimate AUC_{24h} following administration of the standard 5 mg/kg dose of isoniazid. Population pharmacokinetic analysis for appropriate estimation of isoniazid pharmacokinetic parameters was performed in a modelling group ($n = 100$). The Bayesian estimates of AUC_{24h} (AUC_{ref}) obtained for each individual were used as the dependent variable in the regression analysis for the development of various LSS models. The LSS models were validated in a separate cohort ($n = 85$). Several three and four time point LSS models were built and tested. Model H ($AUC_{24h} = -1.88 + 1.05 \times C_1 + 0.78 \times C_2 + 9.44 \times C_5$) and Model I ($AUC_{24h} = -0.65 + 1.00 \times C_1 + 1.94 \times C_2 + 15.45 \times C_9$) had the best performances [adj-$R^2 = 0.93$, median prediction error (MPE) = –0.20, root median squared prediction error (RMSE) = 4.65 for Model H; adj-$R^2 = 0.96$, MPE = –0.05 RMSE = 3.56 for Model I]. The very high R^2 values (≥0.94) of these regression equations in the validation cohort confirmed their high reliability. These LSS models could be applied in the context of therapeutic drug monitoring programmes aiming to personalize isoniazid dosing regimens for adult patients with tuberculosis.

1. Introduction

Tuberculosis (TB) continues to be a global threat, representing the fourth leading cause of death from infectious diseases worldwide [1]. Despite valuable treatment guidelines [2], optimization of drug exposure of first-line antitubercular drugs in each patient remains an issue [3].

Usual pharmacological treatment of TB relies on a combination of four drugs, with isoniazid and rifampicin being the cornerstone drugs. Isoniazid has the highest bactericidal activity, and rifampicin has the most important sterilizing effect [2].

Isoniazid is characterized by wide interindividual pharmacokinetic variability, which is genetically predetermined. This leads to several concerns for treating all TB patients with the same standard dosage of 5 mg/kg [4,5]. Several studies have suggested the need for much higher dosages, up to 16.9 mg/kg, to achieve appropriate drug exposure in fast acetylators [3,6,7]. Low isoniazid plasma levels were associated with treatment failure and the emergence of drug resistance [8,9]. Conversely, significant dosage reductions may be required to avoid the risk of hepatotoxicity among slow acetylators [10,11]. Isoniazid-related hepatotoxicity was shown in 5–33% of patients receiving the standard 5 mg/kg daily dose [12]. Most of these patients are slow acetylators [13,14], in whom poor activity of NAT-2 favours the production of hepatotoxic metabolites, such as hydrazine derivatives [15].

The area under the concentration–time curve (AUC_{24h}) is considered to be the most accurate pharmacokinetic parameter for estimating drug exposure. The AUC_{24h}/minimum inhibitory concentration ratio was found to be a pharmacodynamic determinant associated with both isoniazid bactericidal activity and emergence of resistance [16]. Interestingly, an experimental animal model found that isoniazid bactericidal activity was maximal during the first 14 days of treatment, and decreased dramatically thereafter due to selection of phenotypically tolerant 'persisters' [17]. These findings strengthen the importance of rapid achievement of the target in the early phase of isoniazid treatment in clinical practice in order to minimize resistance.

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Classic estimation of AUC_{24h} based on nine to 10 serial blood collections over a 24-h dosing interval is often unfeasible in daily clinical practice. This limitation may be overcome through the application of validated models of limited sampling strategy (LSS). These models are based on the collection of three to four blood samples over a 24-h dosing interval, and may be validated using appropriate statistical assessment. This approach has been applied to several therapeutic classes [18,19], and has recently been advocated for optimizing antitubercular treatment [20].

The aim of this study was to develop and validate clinically feasible LSS models for estimating isoniazid AUC_{24h} that could be applied easily in daily clinical practice for dosage adjustment in adult patients with TB.

2. Patients and methods

2.1. Study design

Isoniazid plasma concentrations ($n = 1665$) from 185 adult tuberculous patients enrolled in a previous retrospective study [11] were used for the development and validation of LSS models to estimate isoniazid AUC_{24h}. All patients received standard antitubercular treatment with isoniazid, rifampin, pyrazinamide and ethambutol. During the first week of treatment, all patients underwent classic AUC_{24h} assessment of isoniazid as part of the routine drug monitoring approach, as described previously [blood sampling times: before dosing (C_0) and at 0.5 (C_0), 1 (C_1), 2 (C_2), 3 (C_3), 5 (C_5), 7 (C_7), 9 (C_9) and 12 (C_{12}) h after dosing] [11]. All patients received a standard 5 mg/kg/day dose of isoniazid in the morning in a fasted condition. Drug exposure to the other antitubercular drugs was not measured. Although several patients received co-medications due to other underlying diseases, none of these had potential drug–drug interactions with isoniazid.

Patients were assigned at random to two different groups: the modelling group ($n = 100$) and the validation group ($n = 85$). Data from patients included in the modelling group were used to develop a population pharmacokinetic model and to determine different LSS models, the reliability of which was subsequently assessed in the validation group.

2.2. Development of LSS models for isoniazid AUC_{24h} estimation

Population pharmacokinetic analysis for appropriate estimation of isoniazid pharmacokinetic parameters was performed in the modelling group. A one-compartment model was developed with the non-parametric adaptive grid approach included in the Pmetrics package for R (Los Angeles, CA, USA) [21]. A basic model parameterized for clearance and volume of distribution alone was developed. Model evaluation was performed by assessing the goodness of fit by visual inspection of the observed–predicted plot, the coefficient of determination of the linear regression of the observed–predicted values, and the objective function value of each run. Maximum a posteriori probability (MAP)-Bayesian parameter estimates were determined for each patient in the dataset, and were used for describing drug pharmacokinetics in the population. The Bayesian estimates of AUC_{24h} (AUC_{ref}) obtained for each individual were used as the dependent variable in the regression analysis for the development of various LSS models.

All-subsets linear regression analysis of AUC_{ref} against the isoniazid plasma concentration at a specific time point (C_{time}) was undertaken to develop the LSS models. One thousand samples, each made up of 100 arrays of isoniazid concentration–time profiles with their respective AUC_{ref}, were generated by means of bootstrap analysis. A generalized linear model (GLM) with maximum-likelihood estimation and forward inclusion technique was used for determining which C_{time}s could better predict AUC_{ref}. This analysis produced equations of the following form: $AUC_{ref} = int + A_1 \cdot C_1 + A_2 \cdot C_2 + \ldots + A_n \cdot C_n$, where int and A_n are coefficients, and C_n is the drug concentration at the specified sampling time. Consistently, various two, three and four time point LSS models were built by forward inclusion of the selected C_{time}s. All the time point LSS models with $R^2 < 0.5$ were deemed suboptimal and excluded from the study, whereas those with $R^2 \geq 0.5$ were included in the analysis.

2.3. Validation of the LSS models for isoniazid AUC_{24h} estimation

The LSS models developed in the modelling group were validated in the validation group by applying linear regression analysis of the Bayesian estimates of isoniazid AUC_{24h} against the LSS-predicted AUC_{24h}.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to assess whether data were normally or non-normally distributed. Accordingly, mean ± standard deviation or median (interquartile range) were used in the descriptive statistics. Categorical variables were compared using χ^2 test or Fisher's exact test as necessary, while continuous variables were compared using Student's *t*-test or Mann–Whitney test.

The R^2 criteria along with the Akaike information criterion were used to evaluate regression performances. Absolute bias of the predictions was determined by calculating the median prediction error (MPE). MPE is the median of all the differences between the estimated values and the true values, and indicates whether the estimator consistently under- or overestimates the true value. Absolute precision was assessed by calculating the root median squared prediction error (RMSE). RMSE is defined as the squared root of the median of the squared differences between each estimate and the true values. It indicates how close the estimator is to the true value [22].

Bland–Altman plots to visualize the agreement between AUC_{ref} and LSS-derived AUC_{24h} in the modelling group were also reported, as well as Loess statistics to evaluate the correlation between the two AUC_{24h} values in the validation group.

$P \leq 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using Systat Version 13 (Systat Software, Inc., San Jose, CA, USA) and SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

Patients' characteristics are detailed in Table 1. No significant differences were found between the patients included in the two groups. Wide interindividual variability in isoniazid plasma concentrations was observed for post-dose concentrations at each time point, with the coefficient of variation ranging from 40.95% for the 2-h post-dose concentration up to 95.46% for the 12-h post-dose concentration.

Fig. 1 shows the diagnostic plot for the population pharmacokinetics of isoniazid in the modelling group. It is worth mentioning that the final model, after the MAP-Bayesian estimation, explained 97.8% of the variability in drug concentration over time with acceptable bias and precision.

The pharmacokinetic parameters estimated with the final model in the modelling group are reported in Table 2. The mean (range) AUC_{ref} and half-life of isoniazid were 35.11 (7.30136.52) mg·h/L and 2.79 (0.93–8.36) h, respectively.

All post-dose concentrations were significantly correlated with AUC_{ref} in the modelling group, with a correlation coefficient ranging from 0.24 for $C_{0.5}$ up to 0.95 for C_5. At bootstrapping, the C_{time}s showing the highest correlation in predicting AUC_{ref} estimation were, in descending order, $C_{0.5}$, C_1, C_2, C_{12}, C_9 and C_5.