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Limited sampling strategies for therapeutic drug monitoring of amikacin and kanamycin in patients with multidrug-resistant tuberculosis

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ABSTRACT

Amikacin and kanamycin are considered important and effective drugs in the treatment of multidrug-resistant tuberculosis (MDR-TB). Unfortunately, the incidence of toxicity is high and is related to elevated drug exposure. In order to achieve a balance between efficacy and toxicity, a population pharmacokinetic (PPK) model may help to optimise drug exposure. Patients with MDR-TB who had received amikacin or kanamycin as part of their treatment and who had routinely received therapeutic drug monitoring were evaluated. A PPK model was developed and subsequently validated. Using this model, a limited sampling model was developed. Eleven patients receiving amikacin and nine patients receiving kanamycin were included in this study. The median observed 24-h area under the concentration–time curve (AUC_{0-24h}) was 77.2 mg h/L [interquartile range (IQR) 64.7–96.2 mg h/L] for amikacin and 64.1 mg h/L (IQR 55.6–92.1 mg h/L) for kanamycin. The PPK model was developed and validated using $n-1$ cross-validation. A robust population model was developed that is suitable for predicting the AUC_{0-24h} of amikacin and kanamycin. This model, in combination with the limited sampling strategy developed, can be used in daily routine to guide dosing but also to assess AUC_{0-24h} in phase 3 studies.

1. Introduction

Tuberculosis (TB) is a life-threatening disease. Approximately 1.4 million people die as a consequence of this disease every year [1]. Multidrug-resistant TB (MDR-TB) is caused by strains of *Mycobacterium tuberculosis* that are resistant to at least rifampicin and isoniazid. In 2011 an estimated 310 000 of all newly reported TB cases were MDR-TB [1], and in the most recent World Health Organization (WHO) report on TB the incidence of MDR-TB was estimated at ca. 480 000 [2]. Treatment success is associated with a prolonged duration of therapy of a minimum of 18 months with second-line drugs [3].

Amikacin and kanamycin are classified as group 2 (injectable agents) for the treatment of MDR-TB [4]. Recommended dosages are 15–20 mg/kg with a maximum of 1000 mg daily for both amikacin and kanamycin [4]. The reported minimum inhibitory concentrations (MICs) of amikacin and kanamycin are 0.5–1 mg/L and 1–2 mg/L, respectively [5].

The pharmacodynamic (PD) index of aminoglycosides is usually quantified as the ratio of the maximum blood concentration (C_{max}) to the MIC. Aminoglycoside dosing regimens with multiple doses per day were designed to reach certain C_{max} levels, whilst minimising trough blood concentration (C_{min}) levels was required to avoid toxicity. However, in order to detect interindividual and intraindividual differences in clearance or volume of distribution, the area under the concentration–time curve (AUC) might be a more sensitive pharmacokinetic parameter in comparison with the C_{max} or C_{min} [6].

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Interindividual variation in pharmacokinetics may contribute to toxicity and efficacy. Zhu et al. reported that the AUC of streptomycin in 19 patients varied from 124 μg h/mL to 680 μg h/mL, whilst the C_{max} varied from 9 μg/mL to 107 μg/mL [7]. Interindividual variation in C_{max} was also observed for amikacin (median 46 mg/L, range 26–54 mg/L) and kanamycin (median 44 mg/L, range 33–65 mg/L) [8]. This urges the need for a pharmacokinetic model to assess interindividual variability.

Side effects of aminoglycosides are ototoxicity and nephrotoxicity. The prevalence of ototoxicity varies from 18% [9] to 37% [8] and that of nephrotoxicity from 7.5% [9] to 15% [8]. Treatment duration and the cumulative dose were correlated with these side effects, but not the dose or the dosing frequency [8–10]. In addition to the cumulative dose, the cumulative 24-h AUC ($AUC_{0–24h}$) is also related both to nephrotoxicity and ototoxicity [11–13]. A retrospective evaluation of a Dutch cohort showed that a MDR-TB treatment regimen including aminoglycoside drug concentration-guided dosing resulted in high effectiveness with excellent treatment outcome, without severe adverse drug reactions [14]. During the study period, no treatment failures or documented relapses were observed using a relatively low dose of aminoglycosides in an analysis of all MDR-TB patients diagnosed and treated in The Netherlands [14]. A population pharmacokinetic (PPK) model makes it possible to prospectively acquire pharmacokinetic data of aminoglycosides in the treatment of TB in order to design new optimised regimens in the treatment of MDR-TB.

As collecting full blood plasma curves of amikacin or kanamycin to estimate the $AUC_{0–24h}$ and clearance is expensive and burdensome for patients, a limited sampling strategy to perform therapeutic drug monitoring (TDM) will help to improve pharmacotherapy and reduce costs [15]. The objective of this study was to develop a PPK model of amikacin and kanamycin to assess both the $AUC_{0–24h}$ and C_{max} based on retrospective data. This model could be used in a prospective study to evaluate both toxicity and efficacy. Furthermore, a limited sampling strategy will be designed using this pharmacokinetic model.

2. Materials and methods

2.1. Study population

All patients at the Tuberculosis Center Beatrixoord (University Medical Center Groningen, University of Groningen, Groningen, The Netherlands) who were diagnosed with MDR-TB after 1 January 2000 and who met the inclusion criteria were included in this retrospective study. Inclusion criteria included age ≥18 years, treatment with amikacin or kanamycin for longer than 2 days, and availability of at least three plasma concentrations from one dose on the same day. Medical and demographic data were collected from the medical records. Demographic data included age, height and body weight at the start of treatment. Medical data included the aminoglycoside used, the administered dose and serum creatinine (SCr) at baseline. This study was evaluated by the local ethics committee and was allowed according to Dutch law owing to its retrospective nature. Drug susceptibility was determined using the Mycobacteria Growth Indicator Tube (MGIT™) method by the Tuberculosis Reference Laboratory of the National Institute for Public Health and the Environment (RIVM, The Netherlands).

2.2. Pharmacokinetics

Data on the plasma concentrations of the patients included were retrieved from the laboratory information system. Blood analyses were performed by a validated liquid chromatography mass spectrometry (LC–MS/MS) (amikacin and kanamycin) [16] or a validated AxSYM (amikacin) (Abbott, Chicago, IL) method. Both methods were validated on precision and accuracy according to the US Food and Drug Administration (FDA) guidelines [17]. All pharmacokinetic calculations were performed using MW\Pharm 3.81 (Mediware, Groningen, The Netherlands) [18]. Individual pharmacokinetic parameters, including AUC, half-life ($t_{1/2}$), clearance (CL), volume of distribution (V_d) and the elimination rate constant (k_{el}) were calculated using the KinFit module of MW\Pharm using one-compartment analysis.

For amikacin and kanamycin, a model was developed separately using MW\Pharm using a one-compartment model as described previously [19]. We were not able to evaluate the performance of a two-compartment model since there the number of samples at the elimination phase of the curve was insufficient. Differences in pharmacokinetic parameters between both aminoglycosides were analysed using Mann–Whitney *U*-test.

Furthermore, a final model was developed with the amikacin and kanamycin curves combined. The distribution of the parameters of the final model developed was assessed by histograms generated by MW\Pharm. Furthermore, the predicted concentrations were compared with the observed concentrations using residual plots. The influence of the covariates age, weight, height, sex, body surface area (BSA), lean body mass and creatinine clearance (CL_{Cr}) on the renal elimination constant (k_{elr}) and V_d were tested for significance using MW\Pharm. The population parameters of the final model and their 95% confidence intervals (CIs) were calculated using a bootstrap method ($n = 1000$).

The elimination constant was calculated by the following formula: $k_{el} = k_{elm}$ (metabolic elimination rate constant) (fixed to 0) + k_{elr} (renal elimination rate constant) * CL_{Cr} (creatinine clearance in mL/min/1.73 m^2). The free fraction was estimated at 0.04 ± 0.08. The fat distribution was estimated at 0.4. Assay errors were set to 0.1 + 0.035 * [measured concentration], which captured the variation of both methods.

2.3. Limited sampling strategies

A PPK model was developed using the KinPop module of MW\Pharm. This module uses an iterative two-stage Bayesian population procedure [20]. The pharmacokinetic parameters were assumed to be log-normally distributed. The k_{elr} and V_d used to calculate the limited sampling strategies was calculated by the pharmacokinetic model.

Using Monte Carlo simulations, plasma concentrations at eight points in 8 h were calculated for 1000 virtual patients. Only models to optimise AUC were developed. Only practical sampling strategies were evaluated with a minimum time span between two sampling points of 1 h with a maximum of 8 h after administration. Only strategies with a root-mean-squared error (RMSE) of <10% were considered. The ability of the limited sampling model to predict the C_{max} was assessed by entering both the concentrations at 1 h and 4 h combined into the model. The difference between the model-predicted C_{max} and the limited sampling-predicted C_{max} was calculated.

2.4. Statistics

All statistics were performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY). Validation of the pharmacokinetic model developed was performed by calculating new pharmacokinetic models based on experimental data of subsequently $n-1$ patients, which was previously used successfully [21,22]. With this '$n-1$' pharmacokinetic model, $AUC_{0–24h}$ of the excluded patient was calculated. The $AUC_{0–24h}$ calculated with the model was compared with the $n-1$ validation AUC with a Bland–Altman plot. Furthermore, all pharmacokinetic parameters