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Multi-drug resistant tuberculosis in the Netherlands

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c | 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 used in the treatment of multidrug resistant tuberculosis. Unfortunately, the incidence of toxicity is high and related to high drug exposure. To balance between efficacy and toxicity a population pharmacokinetic model may help to optimize drug exposure. MDR-TB patients who had received amikacin or kanamycin as part of their treatment and had routinely received therapeutic drug monitoring were evaluated. A population pharmacokinetic 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. Median observed AUC_{0-24h} was 77.2 (IQR; 64.7– 96.2) mg*h/l for amikacin and 64.1 (IQR; 55.6 – 92.1) mg*h/L for kanamycin. The pharmacokinetic model was developed and validated using n-1 cross-validation. An limited sampling model was developed based on two samples obtained at 1 and 4 hours after administration with an R^2 of >0.99 and a bias and Root Mean Squared Error of -0.04% and 2.5% , respectively. We developed a robust population model 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 III studies.

KEYWORDS: amikacin, kanamycin, tuberculosis, pharmacokinetics, pharmacokinetic model, limited sampling

1. INTRODUCTION

Tuberculosis is a life-threatening disease. Around 1.4 million people die as consequence of this disease every year [1]. Multidrug resistant tuberculosis (MDR-TB) is caused by strains of *Mycobacterium tuberculosis* resistant to at least rifampin and isoniazid. In 2011, an estimated 310,000 of all newly reported TB cases had MDR-TB [1]; and in the most recent WHO report on TB, the incidence of MDR-TB is estimated at around 480,000 [2]. Treatment success is associated with 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 minimal inhibitory concentration (MIC) of amikacin and kanamycin is 0.5-1 mg/L and 1-2 mg/L, respectively [5].

The pharmacodynamic index of aminoglycosides is usually quantified in the maximal blood concentration (C_{max}) divided by the MIC. Aminoglycoside dosing regimens with multiple doses per day were designed to reach certain C_{max} levels, while minimizing C_{min} levels was required to avoid toxicity. However, in order to detect inter- and intra-individual differences in clearance or distribution volume, the area under the curve (AUC) might be a more sensitive pharmacokinetic parameter in comparison with the C_{max} or C_{min} [6].

Inter-individual variation in pharmacokinetics may contribute to toxicity and effectiveness. Zhu et al. claimed that the AUC of streptomycin in 19 patients differed from 124 – 680 µg·hr/ml while the C_{max} differed from 9 – 107 µg/ml [7]. Inter-individual variation in C_{max} was also observed for amikacin (median 46 mg/L, range 26-54 and kanamycin (median 44 mg/L, range 33-65) [8]. This urges the need for a pharmacokinetic model to assess inter-individual variability.

Side effects of aminoglycosides are ototoxicity and nephrotoxicity. The prevalence of ototoxicity varies from 18% [9] to 37% [8] and nephrotoxicity varies from 7.5% [9] to 15% [8]. Treatment duration and the cumulative dose were correlated with these side effects, and not the dose, or the dosing frequency [8-10]. In addition to the cumulative dose, the cumulative AUC_{0-24h} is also related to both nephrotoxicity and ototoxicity [11-13]. A retrospective evaluation of a Dutch cohort showed that an 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, we observed no treatment failures, nor any documented relapses using this relatively low dose of aminoglycosides in an analysis of all MDR-TB patients diagnosed and treated in the Netherlands [14]. A population pharmacokinetic model makes it possible to prospectively acquire pharmacokinetic data of aminoglycosides in the treatment of TB in order to design new optimized 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 (CL) is expensive and burdensome for patients, a limited sampling strategy to perform TDM will help to improve pharmacotherapy and reduce costs [15]. The objective of this study is to develop a population pharmacokinetic 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 (UMCG), University of Groningen, Haren, the Netherlands) who were diagnosed with MDR-TB after January 1st 2000 and met the inclusion criteria were included in this retrospective study. Inclusion criteria included age (≥ 18 years), treatment with amikacin or kanamycin longer than 2 days, availability of at least 3 plasma concentrations from one dose at the same day. Medical and demographic data were collected from the medical records. Demographic data included age, length and body weight at start of treatment. Medical data included the aminoglycoside used, the administered dose and serum creatinine at baseline. This study was evaluated by the local ethics committee (IRB 2013-492) and was according to the Dutch law allowed due 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 concentration of the patients included were retrieved from the laboratory information system. Blood analyses were performed with a validated liquid chromatography mass spectrometry (LC-MS/MS) (amikacin and kanamycin) [16] or with a validated Axsym (amikacin) (Abott, Chicago, IL) method. Both methods were validated on precision and accuracy according to the 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, clearance, distribution volume and the elimination rate constant 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 earlier [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-tests.

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, gender, body surface area, lean body mass and creatinine clearance on the renal elimination constant and distribution volume were tested for significance using MW\Pharm. The population parameters of the final model and their 95% confidence intervals were calculated using a bootstrap method ($n = 1000$).

The elimination constant was calculated by the following formula: $Kel = Kelm$ (metabolic elimination rate constant) (fixed to 0) + $Kelr$ (renal elimination rate constant) * $CLcr$ (creatinine clearance in ml/min/1.73m²). The free fraction was estimated at 0.04 – 0.08. The fat distribution was estimated at 0.4. Assay errors were set to $0.1 + 0.035 * [\text{measured concentration}]$, which captured the variation of both methods.

2.3. Limited sampling strategies

A pharmacokinetic population 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 $Kelr$ and distribution volume $V1$ used to calculate the limited sampling strategies was calculated by the pharmacokinetic model (shown in table 3).

Using Monte Carlo simulations, plasma concentrations at 8 points in 8 hours were calculated for 1,000 virtual patients. Only models to optimize AUC were developed. Only practical sampling strategies were evaluated with a minimum time span between two sampling points of 1 hour with a maximum of 8 hours after administration. Only strategies with an Root Mean Squared Error (RMSE) <10% were considered. The ability of the limited sampling model to predict the C_{max} was assessed by entering both the $T=1$ and $T=4$ concentrations 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 SPSS 22 (SPSS, Virginia, IL). 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 of the n-1 model, including the AUC_{0-24h} , were compared with the population pharmacokinetic model using Wilcoxon Signed Rank tests. Differences in pharmacokinetic parameters between amikacin and kanamycin were assessed using Mann-Whitney U tests. In addition, correlations between demographic and pharmacokinetic data were tested for significance with Spearman correlations or in the case of categorical data with Mann-Whitney U-tests.

3. RESULTS

In total, 30 plasma concentration curves were retrieved from the medical dossiers of 20 patients. Sample times of the individual curves varied between individuals and curves, with a maximum time span of 24 hours. Eleven patients had received amikacin 400 mg once daily, which resulted in 16 plasma concentration curves. In addition, 14 curves were retrieved from nine patients who had received kanamycin 400 mg once daily. The median BMI was 20.3 kg/m² (IQR 18.8 – 22.0), with a median dose per kg body weight of 6.9 mg/kg (IQR 6.3 – 7.8). Demographic data is shown in table 1.

TABLE 1. Patients characteristics.

	Amikacin group (n = 11)	Kanamycin group (n = 9)	P-value
Sex [n (%)]			
Male	5 (45.5)	4 (44.4)	0.66 ^b
Female	6 (54.5)	5 (55.6)	
Height (m)	1.75 (1.68–1.85)	1.62 (1.55–1.69)	0.02 ^c
Weight (kg)	60.0 (57.0–70.4)	51.0 (46.3–58.4)	0.02 ^c
Age (years)	26 (24–43)	31 (24.5–36.5)	0.75 ^c
Dose/kg body weight (mg/kg)	6.67 (5.68–7.02)	7.85 (6.86–8.64)	0.02 ^c
BMI (kg/m ²)	20.2 (19.6–21.4)	20.5 (16.7–23.6)	0.82 ^c
SCr (μmol/L)	64.0 (52.0–68.0)	59.5 (46.5–70.5)	0.88 ^c

BMI, body mass index; SCr, serum creatinine.

^a Data are median (interquartile range) except for sex.

^b Fisher's exact test.

^c Mann-Whitney U-test.

The median AUC_{0-24h} of amikacin (400 mg) was 77.2 (IQR; 64.7 – 96.2) h*mg/L. The median AUC_{0-24h} of kanamycin (400 mg) was slightly lower: 64.1 (55.6 – 92.1) h*mg/L. The coefficient of variation of the AUC_{0-24h} was 33%, indicating that the number of patients included in the model is sufficient to achieve a power level of >80% [23].

TABLE 2. Pharmacokinetic parameters of the population model.

	Median (IQR)		Median (IQR)	
	Amikacin model (n = 16)	Kanamycin model (n = 14)	P-value ^a	Overall model (n = 30)
CL (L/h)	4.62 (4.05–5.35)	5.30 (4.64–5.85)	0.270	5.07 (4.27–5.85)
V_d (L)	12.0 (9.14–15.3)	11.4 (8.50–13.5)	0.423	11.9 (8.70–13.9)
AUC_{0-24h} (h mg/L)	86.7 (75.1–99.0)	75.6 (68.4–86.5)	0.257	79.1 (68.5–93.9)
C_{max} (mg/L)	26.2 (22.7–34.4)	26.6 (24.0–32.7)	0.766	26.6 (23.5–35.9)

IQR, interquartile range; CL, clearance; V_d , volume of distribution, AUC_{0-24h} , 24-h area under the concentration–time curve; C_{max} , maximum serum concentration.

^a Two-tailed exact Mann–Whitney U-test.

Population models of all amikacin and kanamycin curves at 400 mg were first built separately. The pharmacokinetic parameters of these models are displayed in table 2. All parameters were compared using Mann-Whitney U-tests, however, none of the parameter was significantly different between both models.

Therefore, we decided to pool the amikacin and kanamycin curves and to develop a new ‘combined’ model for both amikacin and kanamycin to include more variability in the model in order to increase the robustness of the model. In figure 1, a plot of the amikacin and kanamycin concentration time curves is shown. The population pharmacokinetic parameters and corresponding 95% confidence intervals are shown in table 3. The estimated AUC_{0-24h} was 79.1 (IQR; 68.5 – 93.9) h*mg/L with a C_{max} of 26.6 (IQR; 23.5 – 35.9) h*mg/L. This model was cross-validated using the proposed n-1 methodology. The RMSE in predicting the AUC_{0-24h} , $T_{1/2}$, V_d , CL and C_{max} was 0.36 h*mg/L, 0.004 h, 0.04 L, 0.004 L/h and 0.03 mg/L, respectively. A Bland-Altman plot concerning the AUC_{0-24h} prediction is displayed in figure 2. One outlier was observed, with a deviation of ca. 2 h*mg/L in the AUC_{0-24h} .

TABLE 3. Population pharmacokinetic parameters.

Parameter	Mean (95% CI)	S.D. (95% CI)
k_{elr}	0.00384 (0.00341–0.00432)	0.00143 (0.00113–0.00167)
[h ⁻¹ (mL/min/1.73 m ²) ⁻¹]		
V_d corrected for lean body mass (L/kg)	0.2073 (0.1878–0.2284)	0.0664 (0.0456–0.0858)

CI, confidence interval; S.D., standard deviation; k_{elr} , renal elimination constant; V_d , volume of distribution.

The influence on the covariates age, weight, height, gender, body surface area, lean body mass and creatinine clearance on the renal elimination constant and distribution volume was tested for significance with MW\Pharm. The height ($P = 0.0046$) and creatinine clearance ($P = 0.009$) correlated with the renal elimination constant. In addition, gender ($P = 0.037$) correlated with the distribution volume.

TABLE 4. Limited sampling strategies. ^a

Time point(s) of sampling post-dose	r	Prediction bias (%)	RMSE (%)
2 h	0.984	-3.02	8.6
3 h	0.975	-0.96	10.2
4 h	0.944	0.63	14.9
1 h and 4 h	0.998	-0.04	2.5
1 h and 5 h	0.997	0.03	3.2
1 h and 3 h	0.997	-0.4	3.3
2 h and 4 h	0.996	-0.24	3.8
1 h and 6 h	0.996	0.27	4.1
1, 4 h and 5 h	0.999	-0.09	1.7
1, 4 h and 6 h	0.999	-0.09	1.8
1, 3 h and 5 h	0.999	-0.19	1.8
1, 3 h and 6 h	0.999	-0.19	1.8
1, 2 h and 5 h	0.999	-0.26	1.8

RMSE, root-mean-squared error.

^a Strategies are sorted by RMSE. Only the top five limited sampling strategies with two and three sampling points are shown.

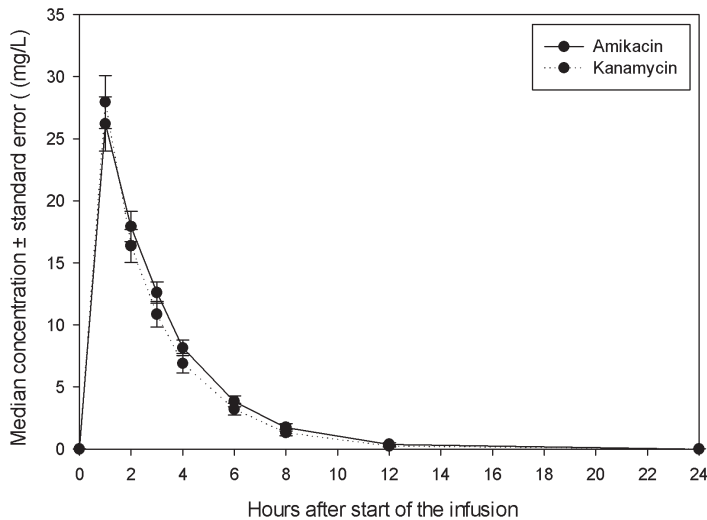


FIGURE 1.

The AUC_{0-24h} , CL, $t_{1/2}$, C_{max} , T_{max} and distribution volume resulting from the $n - 1$ validation were compared with all curves fitted to the population pharmacokinetic model; all parameters showed no difference (AUC : $p = 0.363$, CL : $p = 0.414$, $t_{1/2}$: $p = 0.317$, C_{max} : $p = 0.490$, T_{max} : $p = 1.000$, V_d : $p = 0.472$).

The volume of distribution per kg body weight was higher in men than in women (median: 0.24 vs. 0.19 L/kg, $P = 0.022$, Mann-Whitney U-test). The C_{max} was higher in women (median: 29.2 in women vs. 23.3 mg/L in men, $P = 0.012$, Mann-Whitney U-test); however, the AUC_{0-24h} was not significantly different (median: 78.3 (95% CI: 63.3 – 89.0) in men vs. 86.7 (95% CI: 71.4 – 111.7) h*mg/L in women, $P = 0.285$, Mann-Whitney U-test). Furthermore, volume of distribution, $T_{1/2}$ and the C_{max} correlated with the patients' body weight and height (Spearman correlations, two-tailed test of significance). The AUC_{0-24h} was correlated with the C_{max} computed by the model: $AUC_{0-24h} = 1.636 * C_{max} + 36.190$ with a correlation coefficient (r) of 0.61 using simple linear regression.

Based on the 'combined' population kinetic model, we developed a limited sampling strategy based on a patient with an average weight (59.9 kg), height (1.68 m) and serum creatinine (63 mmol/L) and 35 years of age. Different limited sampling strategies were evaluated and subsequently the RMSE, bias and correlation coefficient of the AUC were calculated. These different limited sampling strategies are displayed in table 4. The RMSE is the most important parameter, since this indicates the precision in the prediction of the AUC_{0-24h} . Sampling at 1 and 4 after start of the infusion resulted in an RMSE of 2.5% with a

prediction bias of -0.04%, respectively. The Cmax calculated by the model was compared with the Cmax calculated by the model based only on the concentrations at T=1 and T=4. The median difference was -0.04% (IQR; -0.28 – 0.38%).

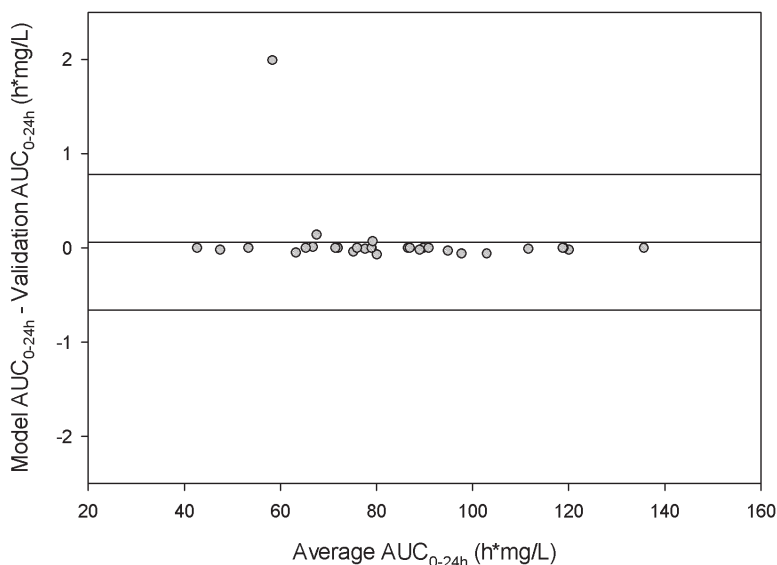


FIGURE 2.

4. DISCUSSION

We developed the first limited sampling strategy of amikacin and kanamycin in patients with tuberculosis. The RMSE found in predicting the AUC_{0-24h} from samples at 1 and 5 hours is very low (2.9%). The model was successfully validated using the proposed n-1 cross-validation methodology. Since none of the relevant pharmacokinetic parameters showed a significant difference between amikacin and kanamycin, the final pharmacokinetic model was identical for both drugs. This model was considered appropriate for the assessment of individual pharmacokinetics during daily patient care. Furthermore, this limited sampling model could be used to assess drug exposure in randomized controlled trials evaluating efficacy of new regimens in the treatment of TB.

The pharmacokinetic parameters of the population model are higher than those in neutropenic patients (CL 5.07 vs. 4.43 L/h, Vd 11.9 vs. 8.92 L). This could be due to the use of a two-compartment model, while we used a one-compartment model. The authors found that the one-compartment model was unable to fit peaks and 12-24h trough levels. However, our model did not seem to have this disadvantage. [24]. We evaluated

2-compartment models which provided a slightly better fit to our data, however, these models provided unrealistic curves between 12 and 24 hours post-dose. A 1-compartment model did not seem to have this disadvantage.

The distribution volume per kg body weight of critically ill patients is higher (0.39 – 0.45 L/kg vs. 0.20 L/kg in this study) [25]. However, these critically ill patients were experiencing sepsis or a septic shock, and gained volume during the first hours of resuscitation explaining the higher distribution volume. A study with healthy volunteers showed that the pharmacokinetic parameters of amikacin are comparable with our population, except for the clearance, which is slightly lower in our population (V_1 11.0-11.15 vs. 11.9 L, CL 6.8-7.6 vs. 5.07 L/h, depending on the amikacin dose of 7.5 or 15.0 mg/kg) [26]. This difference in clearance might be caused by the nephrotoxic potential of these aminoglycosides during an extended period of time or the simultaneous administration of other antibiotics in the treatment of TB. Due to the differences in population pharmacokinetics, it may be necessary to re-evaluate the proposed limited sampling strategy in other populations. The distribution volume and C_{max} appeared to be significantly different between genders. As women have commonly a higher percentage body fat in comparison to men, and aminoglycosides are very hydrophilic, this is an understandable correlation. In addition, the height and weight of women is generally lower than in men, which also affects the C_{max} and V_d . When targeting a certain C_{max} level, this would result in lower dosages for women, while the AUC_{0-24h} was not significantly different between both genders.

Using the AUC/MIC ratio instead of the C_{max}/MIC -ratio to monitor efficacy needs to be validated in an *in vitro* model for infection [27] and subsequently tested in a prospective clinical trial. Nevertheless, evidence in animal models suggests that the AUC_{0-24h}/MIC ratio predicts the efficacy of the aminoglycoside therapy [28], and we speculate that this ratio can also be applied to humans [29]. But this needs to be confirmed in a hollow fiber model as has already been done for moxifloxacin [27].

In our TB center, drug concentration-guided dosing of aminoglycosides is daily routine. The average dose given is 6.7 mg/kg, which is lower than the dose recommended by the World Health Organisation of 15 – 20 mg/kg [4]. Within our center, aminoglycoside dose is based on individualised treatment based on the C_{max}/MIC ratio [30,31]. A retrospective study was performed to evaluate the treatment outcome with a treatment regimen incorporating this lower TDM-guided dosing and showed favourable results [14]. It should however be noted that an additional prospective study is necessary to confirm the efficacy of this relatively low dosage.

Although common practice, estimating the AUC_{0-24h} with only a peak-level measurement (C_{max}) appears to be unreliable with a correlation coefficient of only 0.61. The addition of a trough level 24 hours post-dose did not improve this estimation. However, measuring at 1 and 5 hours post-dose resulted in a high correlation of >0.99 and a low RMSE and bias. In

addition, a fair estimation of the AUC_{0-24h} could be based on a one-point estimate 3 hours post-dose.

Oral drugs used in the treatment of MDR-TB show strong correlations between the AUC_{0-24h} and the serum concentration 6 hours post dose [32]. The AUC_{0-24h} of aminoglycosides can be easily predicted with the sample times used to assess the exposure of oral drugs. With this strategy, the estimation of the AUC_{0-24h} of several anti-TB drugs with only two or three samples is possible.

Fluoroquinolones and aminoglycosides are the cornerstone of MDR-TB treatment, however, resistance development and toxicity are causes for concern. Treatment with fluoroquinolones, such as moxifloxacin, can be optimized using PK/PD modelling [22]. With this work we have shown that the assessment of the aminoglycoside exposure using a limited sampling strategy is accurate. This limited sampling strategy provides a good estimation of the AUC_{0-24h} and is therefore suitable for use in outpatient clinics, but also during TDM in prospective clinical trials.

5. CONCLUSIONS

This study showed that the AUC_{0-24h} of amikacin and kanamycin can be predicted using a limited sampling strategy in combination with the developed population pharmacokinetic model. This strategy can be used to optimize TB treatment by reducing toxicity while maintaining efficacy but may also be included in phase III studies to collect data on drug exposure.

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