의학석사 학위논문

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2020 년 8 월

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ABSTRACT

Population pharmacokinetic analysis of amikacin for optimal pharmacotherapy in adult patients with nontuberculous mycobacterial pulmonary disease

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Introduction: Nontuberculous mycobacteria (NTM) belongs to mycobacterial species other than organisms of the mycobacterium tuberculosis. Nontuberculous mycobacterial pulmonary disease (NTM-PD) is the most common infection disease of NTM. Amikacin is used as a therapy for patients with NTM-PD who are resistant to macrolide antibiotics or have severe symptoms. Although the population pharmacokinetic analysis of amikacin has already been performed in various

patient populations, the population pharmacokinetic analysis of amikacin has not been conducted in patients with NTM-PD. Therefore, this study aimed to characterize the PK properties of amikacin in patients with NTM-PD and to develop a PK model to determine the optimal pharmacotherapy in patients with NTM-PD.

Methods: In this study, amikacin concentration-time data were obtained during routine therapeutic drug monitoring. The SUPREME, clinical data warehouse system was used to retrospectively collect the amikacin dosing regimen, serum amikacin concentrations, blood sampling times, serum creatinine, serum albumin, and patient demographics for patients with NTM-PD. The patients with NTM-PD received single or multiple intravenous doses of amikacin. Amikacin concentrations were collected for 70 adult patients with NTM-PD and 848 serum concentrations were available for analysis. A population pharmacokinetic model was developed using nonlinear mixed-effects modelling. A model-based simulation was performed to obtain the optimal pharmacotherapy of amikacin in patients with NTM-PD.

Results: A two-compartment model with first order elimination best described the amikacin pharmacokinetics. The estimated glomerular filtration rate (eGFR) and body weight were identified as covariates for clearance and volume of distribution, respectively. Serum amikacin concentration decreased with an increase body weight when amikacin was administered at the same dosage regimen for various body weight. The proposed eGFR-guided dosing regimens were 12 mg/kg once daily for patients with normal renal function and 11 mg/kg once daily for patient with eGFR below 90 mL/min/1.73m^2. In the intermittent dosing regimen, the proposed eGFR-guided dosing regimens were 22 mg/kg for patients with an eGFR of 60 mL/min/1.73m^2 or more and 21 mg/kg for patients with an eGFR below 60 mL/min/1.73m^2.

Conclusion: This is the first study to perform a population pharmacokinetic analysis of amikacin to determine the optimal pharmacotherapy in adult patients with NTM-PD. Based on the final developed model, optimal pharmacotherapy was suggested to be dependent on the renal function of patients with NTM-PD,

allowing the personalization of drug therapy for amikacin that will improve clinical outcomes of amikacin therapy.

Keywords: Nontuberculou mycobacterial pulmonary disease; amikacin; population pharmacokinetics

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INTRODUCTION

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is a chronic pulmonary disease caused by infection with nontuberculous mycobacteria (NTM).[1] NTM are also known as atypical mycobacteria, mycobacteria other than tuberculosis, which are normally present in the environment.[2] NTM can produce clinical diseases in any body tissue, such as pulmonary disease, lymphatic and skin/soft tissue; and the most common manifestation of NTM disease is pulmonary disease.[3] Although NTM encompass more than 200 species of bacteria, pulmonary infections are commonly due to *Mycobacterium avium complex*, *Mycobacterium abscessus*, *Mycobacterium kansasii* in South Korea.[1, 2] Macrolide antibiotics form the basis of therapy for NTM-PD, and patients with macrolide resistance or severe NTM-PD are treated with amikacin.[4]

Amikacin is an aminoglycoside antibiotic that is used for the treatment of severe infection with multidrug-resistant, aerobic Gram-negative bacteria, which bind to bacterial 30S ribosomal subunits and lead to the disruption of normal protein synthesis and the production of non-functional or toxic peptides.[5] Therefore, amikacin is used for the treatment of NTM-PD. With

regard to the pharmacokinetic (PK) characteristics of amikacin, the half-life is approximately 2 h, and less than 11% of amikacin is actually bound to plasma proteins.[6, 7] The vast majority of amikacin is secreted unchanged via glomerular filtration.[7] Amikacin showed concentration-dependent killing of bacteria and the pharmacodynamic target was a ratio of ≥ 8 between the peak concentration (C_{peak}) and the minimal inhibitory concentration (MIC) of the bacteria.[8, 9] The utility of amikacin is limited owing to its well-known adverse effects such as nephrotoxicity and ototoxicity. The occurrence of amikacin adverse events is associated with a variety of factors including C_{peak}, trough serum concentration (C_{trough}), treatment duration, and cumulative dose.[5] Therefore, in general, to achieve sufficient effects while reducing the toxicity, the guidelines recommend that C_{peak} should be adjusted to less than 35 μg/mL and that C_{trough} should be less than 10 μg/mL.[10] However, for the indication of NTM-PD, the target concentration is higher than that for other indications; the guideline recommend that C_{peak} should be adjusted to 35-45 μg/mL with once-daily administration, that the C_{peak} should be adjusted to 65-80 μg/mL for intermittent dosing regimen, and that C_{trough} should be

maintained at less than 4 μg/mL in both dosing regimens.[10, 11] Another guideline stated that for patients with NTM infection, intravenous (IV) amikacin should be administered at a dose of 10–15 mg/kg daily, and that 25 mg/kg was also reasonable when administered three times per week.[4] Despite these guidelines, several studies indicated that amikacin toxicity was observed in 3.3% to 40.2% of patients with NTM–PD.[12–14]

The prevalence and incidence of NTM–PD have increased globally, including in Korea.[15–17] Because of the toxicity and narrow therapeutic range of amikacin, more specific and accurate dosage recommendations than the above guidelines are needed. The PK profile of amikacin has not been evaluated in patients with NTM–PD. Therefore, the aims of this study were to evaluate the PK properties of amikacin in patients with NTM–PD by using population PK analysis and to explore the target attainment regimen through a model–based simulation.

MATERIALS & METHODS

Study population

Data were collected retrospectively from patients who received IV amikacin for NTM-PD treatment at the Seoul National University Hospital (SNUH) between 1st December 2009 and 1st December 2019. Patients were included if both amikacin dosage and serum concentration-time records were available. This study was reviewed and approved by the Institutional Review Board at SNUH, Seoul, Republic of Korea.

Data collection

In the study, data were collected retrospectively from SUPREME which is the clinical data warehouse (CDW) system of SNUH. Amikacin was administered by IV infusion over 30 min or 1 h at intervals of 8, 12, 24, or 48 h. Blood samples were taken for patients' therapeutic drug monitoring (TDM), therefore, amikacin serum concentrations were obtained after first dose and/or after steady state. Most of the blood sampling for C_{peak} measurements was obtained within 60 min after the amikacin infusion was completed, and most of C_{trough} were obtained within 30 min prior to the next infusion (Figure 1). Amikacin

concentrations that below the limit of quantitation were excluded from the analysis. The patient's age, sex, weight (WT), height (HT), serum creatinine concentration (SCR) and serum albumin (ALB) concentration at the closest time before TDM sampling were collected from electronic medical record (EMR). The estimated glomerular filtration rate (eGFR) was computed by using the MDRD formula.

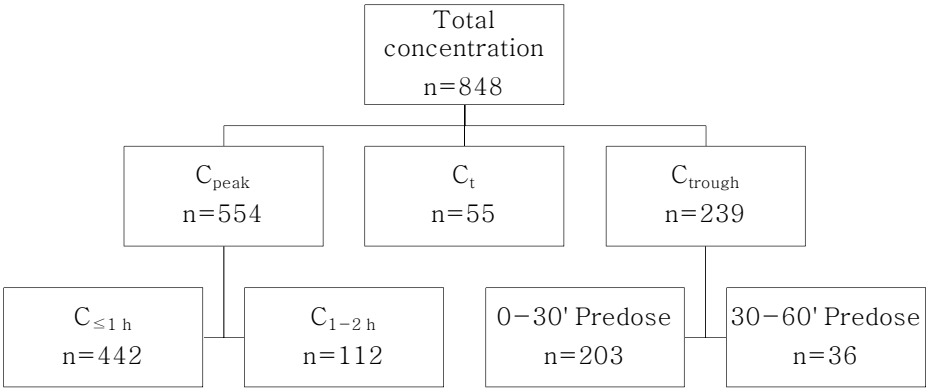

Figure 1. Number of amikacin serum levels in relation to blood sampling times. (C_t is represent sampling times other than those specified in the figure).

Population pharmacokinetic analysis

All concentration-time data collected were used for this population PK analysis. A population PK analysis from logarithmically transformed concentration data was performed using a nonlinear mixed effects method in NONMEM (version 7.4.3, Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction option was used throughout the analysis.

For the structure model, one- and two- compartment PK models with linear elimination model were tested. The inter-individual variability (IIV) of the PK parameters was consider exponentially, as follows:

$$P_i = P \cdot \exp(\eta_i)$$

where P_i is the value of the parameter for the i^{th} subject, P represents the population typical value of the parameter, and η_i is a random variable of parameter for the i^{th} subject following a normal distribution with a mean of 0 and variance of ω^2. The combined additive and proportional models were used to describe intra-individual variability. In the model, the OMEGA BLOCK option was used to reflect the correlation between random variables.

The selection of the PK base model structure was based on goodness-of-fit (GOF) plots, the precision of numerical estimates, and the decrease in objective function value (OFV).

Covariate selection

After selection of the PK base model, a graphical approach was used to screen the potential covariates. For visual screening, scatterplots of individual PK parameters versus covariates were used. After the covariate screening step, covariates were then tested by stepwise forward selection and backward elimination using NONMEM and the PsN toolkit on the criteria of the OFV with significance set at $P < 0.05$ (forward) and $P < 0.01$ (backward). The following covariates were evaluated for inclusion: age, WT, HT, SCR, ALB, and eGFR as continuous covariates and sex as categorical covariates. For continuous covariates, both linear and power relationships were tested, whereas categorical covariates were tested using a categorial model.

$$P = \theta_1 \cdot (1 + \theta_2 \cdot [COV - MED])$$

$$P = \theta_1 \cdot (\frac{COV}{MED})^{\theta_2}$$

$$P = \theta_1 \cdot (1 + \theta_2 \cdot [IND])$$

where P was the individual's estimate of the parameter, θ_1 represented the typical value of the parameter, θ_2 represented the effect of the covariate, and MED was the population median

of the covariates, IND was an indicator variable with a value of either 0 or 1 assigned for values of categorical covariate (0: female; 1: male). In addition to the statistical criteria, decrease in IIV and physiological plausibility were considered for covariate inclusion in the model.

PK model validation

After model development, the final model was diagnosed by GOF plots, bootstrap analysis, and prediction-corrected visual predictive check (pc-VPC). The GOF plots consisted of the following four plots: observations versus individual predictions; observations versus population predictions; conditional weighted residuals versus population predictions; and conditional weighted residuals versus time after dose. pc-VPC was used to confirm that the observed data points were overlaid within the median and 90% confidence intervals of 1000 simulated datasets from the final model. The bootstrap median parameter values and 95% percentile intervals were compared with those estimated from the original data set using the final model.

Regimen exploration by simulation

Based on the final developed model, model-based simulations were performed to predict the amikacin concentrations after

multiple doses of various dosing regimens. The simulated dosing regimens included once-daily dosing and intermittent (every other day; q48h) dosing of five doses, ranging between 9 mg/kg and 15 mg/kg, and 17 mg/kg and 25 mg/kg, respectively. A period of 5 days was considered a sufficient time to reach steady state. As specified by the amikacin dosing guidelines for once daily dosing, C_{peak} was within 35-45 μg/mL and C_{trough} was less than 4 μg/mL, which was classified as the therapeutic range, and for intermittent dosing, C_{peak} was within 65-80 μg/mL and C_{trough} was less than 4 μg/mL, which was classified as the therapeutic range. Therefore, based on the target therapeutic range, the probability of reaching the therapeutic range during various dosing regimens was calculated.

RESULTS

Demographic characteristics

In total, 848 serum amikacin concentration–time data were collected from 70 adult patients who received amikacin for the treatment of NTM–PD. Of the analyzed patients, 51 (73%) were females and 19 (27%) were males. The patients were between 25 and 85 years of age, and the body weight ranged from 29.90 to 79.80 kg (Table 1).

Table 1. Demographic characteristic of patients.

Variable	Female (N=51)	Male (N=19)
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)
Age (years)	63.46±8.82 (45.00 – 84.00)	71.78±11.65 (25.00 – 85.00)
BMI (kg/m^2)	20.34±3.37 (13.67 – 33.33)	20.72±4.22 (12.78 – 26.21)
Height (cm)	156.30±6.14 (146.10 – 167.00)	170.34±5.27 (161.60 – 177.00)
Weight (kg)	49.43±7.80 (29.90 – 74.00)	59.94±13.14 (38.70 – 79.80)
Serum creatinine (mg/dL)	0.67±0.15 (0.30 – 1.86)	0.84±0.26 (0.29 – 1.59)
eGFR* (mL/min/1.73m^2)	94.48±28.18 (26.80 – 253.70)	104.57±47.89 (46.00 – 297.80)
Albumin (g/dL)	3.70±0.50 (1.60 – 4.80)	3.32±0.48 (1.90 –4.30)

SD, standard deviation

* Calculated using MDRD formula, $eGFR = 175 \times Serum\ creatinine^{-1.154} \times Age^{-0.203} \times [0.742\ if\ female]$

Population pharmacokinetic model

The two-compartment model was more suitable than one-compartment model, but in conditional weighted residuals (CWRES) versus time plots, diagnostic plots, the scatter plots were focused on the positive value, and this was improved when the concentration value was replaced with the natural logarithmic value. Finally, a two-compartment model with first-order elimination kinetics provided the best description of amikacin PK. IIV was described by an exponential error model and CL and V1 were estimated. The base PK model included an ω block to assess covariance among CL and V1, as this approach improved model fitting, and the ω block was retained in the final model (Figure 2).

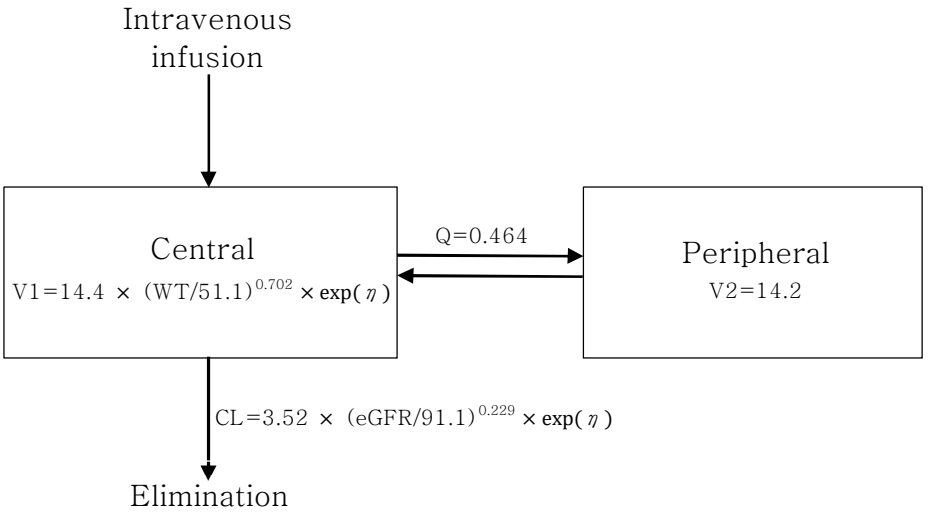

Figure 2. Schematic diagram of the final amikacin pharmacokinetic model.

Covariate evaluation was also conducted. eGFR and body weight were identified as significant covariates (Table 2). The OFV was significantly reduced when serum albumin was added to CL and V1 as a covariate; however, there was a positive relationship and negative relationship with CL and V1, respectively. Thus, serum albumin was excluded from the covariate because the relationship was not physiologically valid.

The estimated population CL was 3.52 L with 27.9% IIV at the population median eGFR of 91.1 mL/min/1.73m^2 and V1 was 14.4 L with 18% IIV at the population median body weight of 51.1 kg. To determine the impact of body weight on the V1 of amikacin, the lowest (29.9 kg) and highest (79.8 kg) body weights obtained from the PK analysis data were used to calculate the V1 of amikacin; the results showed the V1 of the highest body weight was 1.99 times larger than the lowest body weight. In the same way, to determine the effect of eGFR on amikacin clearance, the highest eGFR (297.8 mL/min/1.73m^2) was 1.74 times greater than lowest eGFR (26.8 mL/min/1.73m^2).

Table 2. Sequential covariate model development.

Model	Hypothesis	⊿OFV	Basis of model	% IIV for CL (% RSE)	% IIV for V1 (% RSE)
0	Base model	–	–	30.4 (10)	21.9 (11)
1	$TVCL=\theta_1*(eGFR/91.1)^{\theta_2}$	−27.348	0	28.3 (10)	22.4 (10)
2	$TVCL=\theta_1*(1+(eGFR/91.1)*\theta_2)$	−19.400	0	28.8 (10)	22.3 (10)
3	$TVCL=\theta_1*(WT/51.1)^{\theta_2}$	−6.969	0	28.9 (11)	22.0(10)
4	$TVCL=\theta_1*(1+(WT/51.1)*\theta_2)$	−6.416	0	29.0 (11)	22.0 (10)
5	$TVCL=\theta_1*(ALB/3)^{\theta_2}$	−25.922	0	29.1 (12)	22.2 (10)
6	$TVCL=\theta_1*(1+(ALB/3)*\theta_2)$	−28.412	0	29.2 (12)	22.2 (10)
7	$TVCL=\theta_1*(1+(SEX)*\theta_2)$	−3.663	0	30.2 (11)	22.0 (10)
8	$TVV1=\theta_1*(eGFR/91.1)^{\theta_2}$	−4.812	0	30.4 (10)	22.5 (11)
9	$TVV1=\theta_1*(1+(eGFR/91.1)*\theta_2)$	−3.530	0	30.4 (10)	22.1 (10)
10	$TVV1=\theta_1*(WT/51.1)^{\theta_2}$	−22.806	0	30.2 (10)	17.5 (11)
11	$TVV1=\theta_1*(1+(WT/51.1)*\theta_2)$	−23.508	0	30.4 (10)	22.1 (10)
12	$TVV1=\theta_1*(ALB/3)^{\theta_2}$	−24.674	0	30.5 (10)	19.6 (9)
13	$TVV1=\theta_1*(1+(ALB/3)*\theta_2)$	−29.712	0	30.5 (10)	19.5 (10)
14	$TVV1=\theta_1*(1+(SEX)*\theta_2)$	−22.859	0	30.5 (10)	17.5 (14)
15	$TVCL=\theta_1*(eGFR/91.1)^{\theta_2}$, $TVV1=\theta_3*(WT/51.1)^{\theta_4}$	−20.368	1	27.9 (10)	18.0 (12)

⊿OFV: change in objective function value; IIV: interindividual variability; RSE: relative standard error; TV: typical value; CL: clearance; V1: central compartment volume; eGFR: estimated glomerular filtration rate; WT: weight; ALB: serum albumin; θ_1: typical value of the PK parameter.

Model validation

The GOF plots showed a good agreement between the observations and predictions in the final developed model. CWRES were dispersed around 0 and did not show any relevant trends (Figure 3). The pc-VPC plots also showed good adequacy between the observed and the predicted amikacin concentration (Figure 4). The values estimated through the bootstrap analysis and the final model were similar (Table 3).

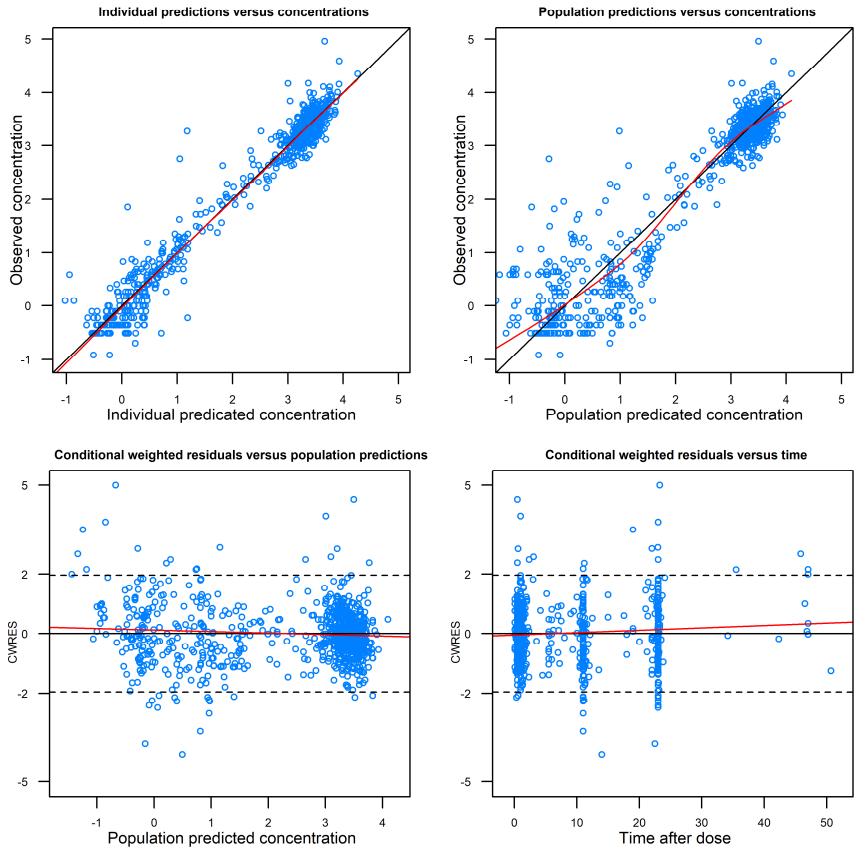

Figure 3. Goodness-of-fit plots of the final pharmacokinetic model. Open circles indicate observations; solid black lines are lines of identity; dotted line, the line of reference; red line, the line of locally weighted scatterplot smoothing.

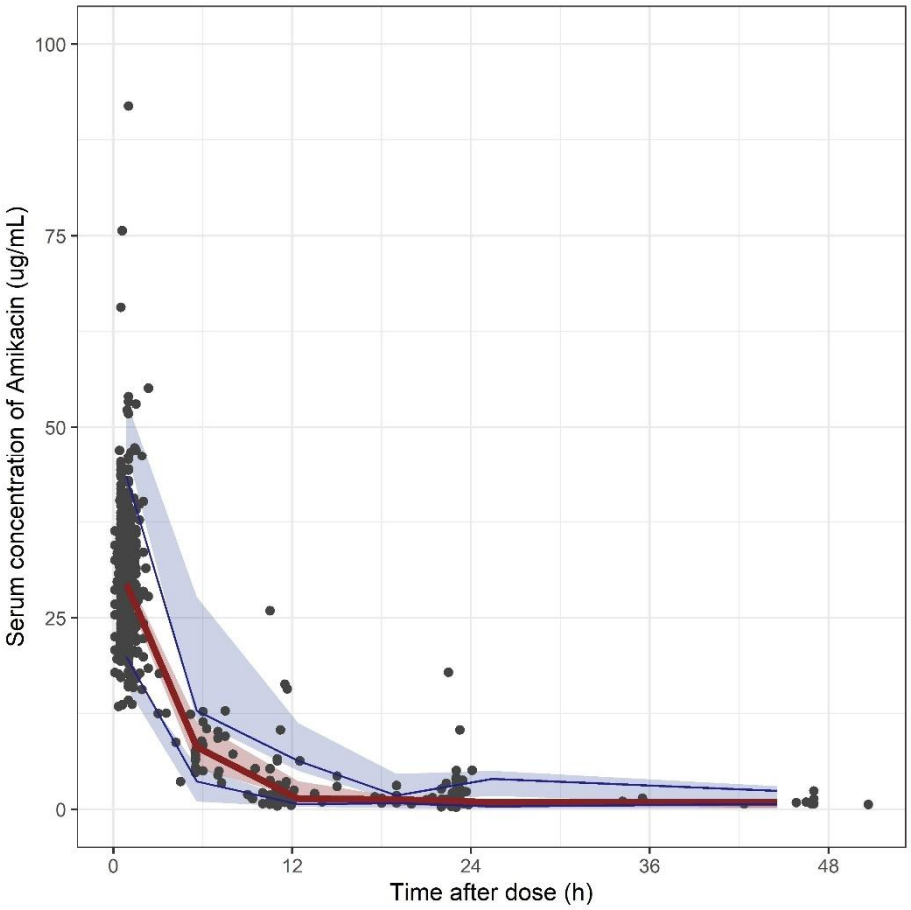

Figure 4. Prediction-corrected visual predictive check for the final population pharmacokinetic model. In total 1000 datasets were simulated using the final PK parameter estimates. The solid circles represent the observed amikacin plasma concentrations. Blue and red areas indicate the 90% confidence interval of the simulated concentrations, and the solid lines represent the 5th (blue line), median (red line), 95th (blue line) of the observed concentration.

Table 3. Pharmacokinetic and covariate parameters in the base and final population models.

Parameter	Based model (OFV= −899.01)		Final model (OFV= −943.678)		Bootstrap (n=1000)
	Estimate (% RSE)	IIV (% RSE)	Estimate (% RSE)	IIV (% RSE)	Median (95% CI)
CL (L/h)	3.5 (5)	30.4% (10)	3.52 (5)	27.9% (10)	3.527 (3.219−3.789)
~eGFR	−	−	0.229 (32)	−	0.228 (0.051−0.331)
V1 (L)	14.5 (4)	21.9% (10)	14.4 (4)	18% (12)	14.297 (13.462−15.250)
~WT		−	0.702 (17)	−	0.681 (0.472−0.897)
V2 (L)	16.4 (35)	−	14.2 (34)	−	14.864 (8.946−41.629)
Q (L/h)	0.443 (24)	−	0.464 (25)	−	0.477 (0.318−0.685)
Covariance (CL and V1)	0.00623	−	−0.0135	−	−0.012 (−0.289−0.006)
Residual error (additional)	0.303 (8)	−	0.299 (8)	−	0.294 (0.254−0.331)

OFV, objective function value; IIV, interindividual variability; RSE, relative standard error; CI, confidence interval; CL, clearance; eGFR, estimated glomerular filtration rate; V1, central compartment volume; WT, weight; V2, peripheral compartment volume; Q, intercompartmental clearance.

Dosing regimen recommendation

To confirm the effect of body weight on amikacin concentration, a simulation was conducted examining five times doses of amikacin 500 mg once-daily for individuals of various body weights (30-120 kg) with normal renal function (90 mL/min/1.73 m^2). The C_{peak} of amikacin decreased as the body weight increased when amikacin was administered with the same dosing regimen. The mean C_{peak} of amikacin in the lightest patients and the heaviest patients differed by approximately 2.5 times (Figure 5). Therefore, in the case of amikacin, weight-based dosing in patients is appropriate.

Based on the final model, the concentration-time profiles of amikacin following five IV infusions of various dosing regimens (9-15 mg/kg, q24h; 17-25 mg/kg, q48h) were simulated based on renal function. Renal function was classified by using the following criteria: grade 1, eGFR≥90 mL/min; grade 2, 60≤eGFR≤89 mL/min; grade 3, 30≤eGFR≤59 mL/min; grade 4, 15≤eGFR≤29 mL/min; grade 5, eGFR<15 mL/min. For patients with normal renal function, 12 mg/kg was the most suitable dose regimen and for patients with the other grade of renal function, 11 mg/kg once-daily dosing was more suitable

(Figure 6, Table 4). However, for patients with grade 2 and 3 renal function, the probability of therapeutic target attainment was the highest in the 12 mg/kg once-daily dosing regimen, the probability of toxic concentrations occurring was increased by 10%. Overall, the 11 mg/kg once-daily regimen was more suitable than 12 mg/kg in patients with eGFR below 90 mL/min/1.73 m^2. In the intermittent dosing regimen, the 22 mg/kg q48h regimen was suitable for patients with grade 1, or 2 renal function, and the 21 mg/kg q48h regimen was suitable for patients with grade 3,4, or 5 renal function (Figure 7, Table 5).

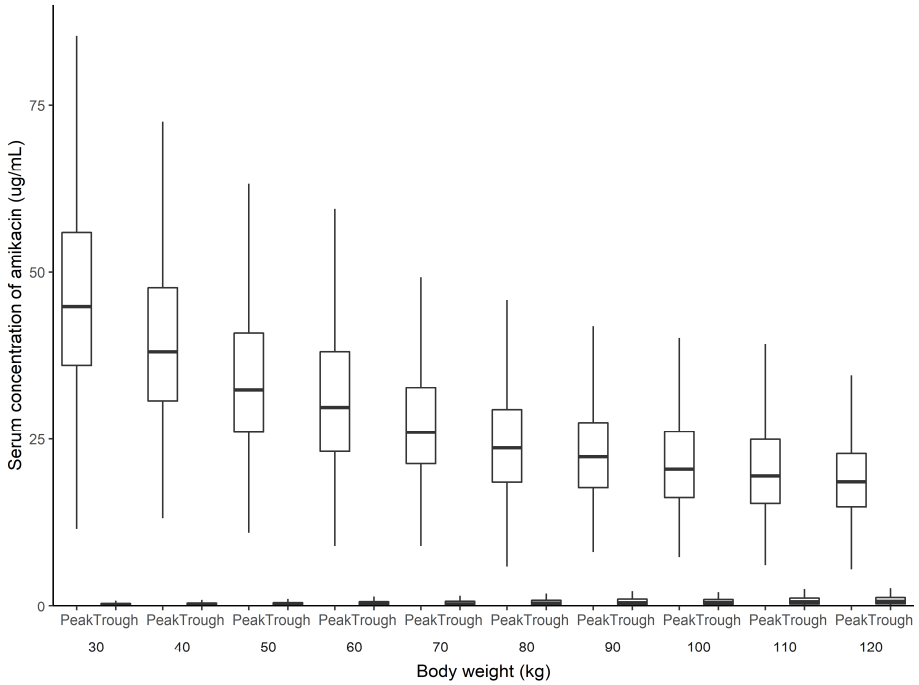

Figure 5. Box plot of predicted amikacin concentration following 5 times amikacin intravenous administration with 500 mg once daily dosing regimen in various body weight patients with normal renal function.

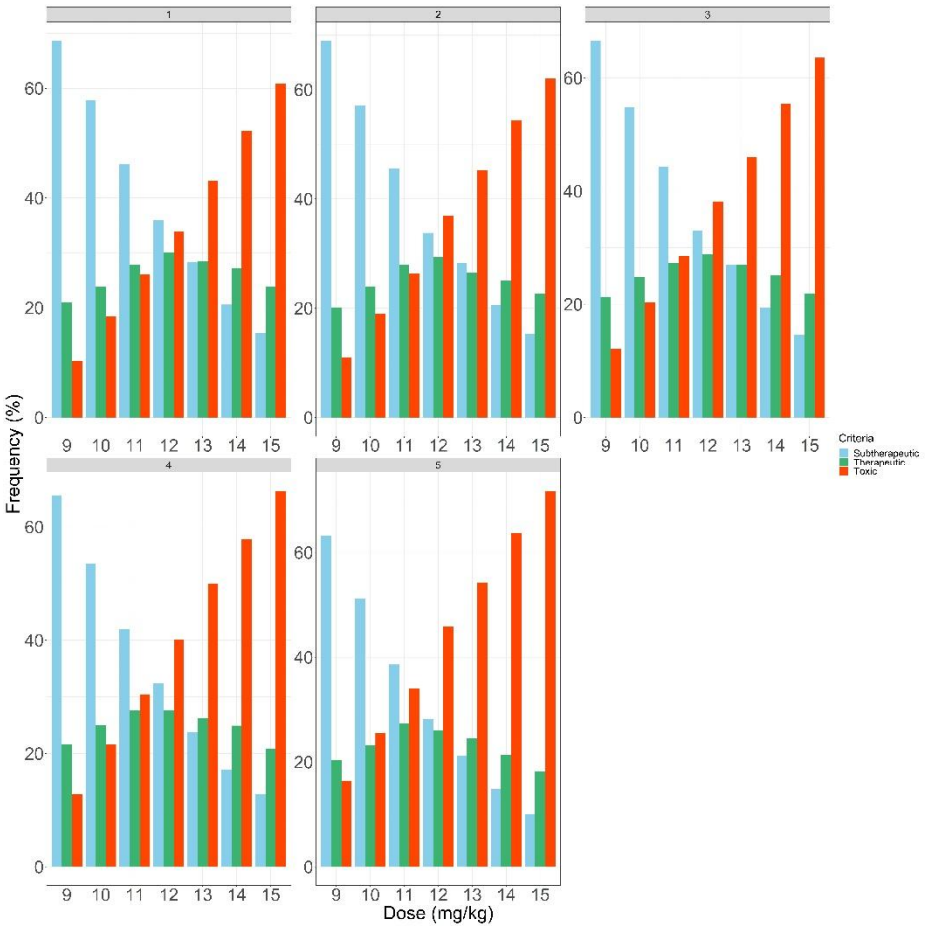

Figure 6. Probability of amikacin therapeutic target attainment from model-based simulations of amikacin pharmacokinetic profiles after the following 5 times administration with amikacin IV once daily dosing regimens. Left axis represents the grade of renal function. Grade of renal function classified as follows: 1, eGFR≥90; 2, 60≤eGFR≤89; 3, 30≤eGFR≤59; 4, 15≤eGFR≤29; 5, eGFR<15.

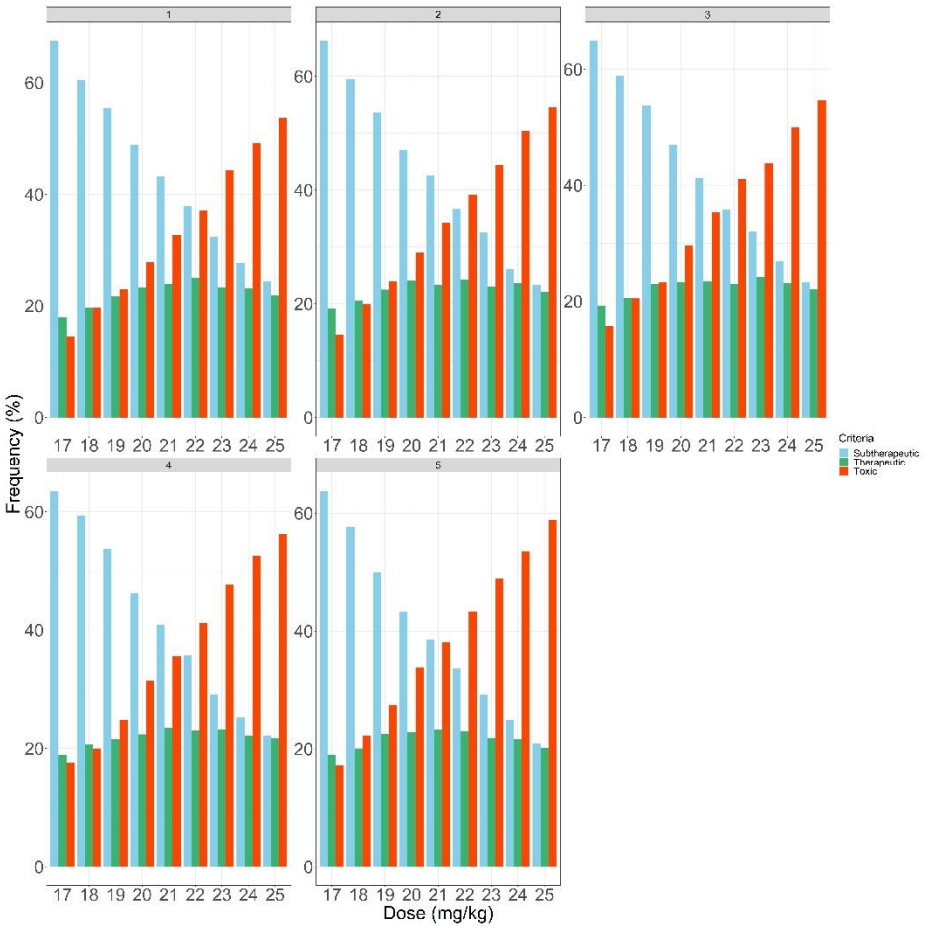

Figure 7. Probability of amikacin therapeutic target attainment from model-based simulations of amikacin pharmacokinetic profiles after the following amikacin IV intermittent dosing (q48h) regimens on day 5. Left axis represents the grade of renal function. Grade of renal function classified as follows: 1, eGFR≥90; 2, 60≤eGFR≤89; 3, 30≤eGFR≤59; 4, 15≤eGFR≤29; 5, eGFR<15.

Table 4. Probabilities of target attainment from model-based simulation of amikacin pharmacokinetic profiles followed 5 times administration of amikacin by various once daily dosing regimen.

Grade[a]	Target attainment[b]	9 mg/kg	10 mg/kg	11 mg/kg	12 mg/kg	13 mg/kg	14 mg/kg	15 mg/kg
1	Subtherapeutic	68.66	57.74	46.16	35.96	28.28	20.58	15.36
	Therapeutic	20.98	23.88	27.82	30.10	28.52	27.18	23.82
	Toxic	10.36	18.38	26.02	33.94	43.20	52.24	60.82
2	Subtherapeutic	68.96	57.16	45.62	33.80	28.28	20.64	15.32
	Therapeutic	20.06	23.90	28.00	29.32	26.52	25.04	22.68
	Toxic	10.98	18.94	26.38	36.88	45.20	54.32	62.00
3	Subtherapeutic	66.58	54.88	44.24	33.00	26.94	19.44	14.58
	Therapeutic	21.34	24.78	27.28	28.80	27.00	25.16	21.86
	Toxic	12.08	20.34	28.48	38.20	46.06	55.40	63.56
4	Subtherapeutic	65.60	53.44	41.92	32.34	23.80	17.20	12.86
	Therapeutic	21.56	25.02	27.62	27.58	26.22	24.92	20.78
	Toxic	12.84	21.54	30.46	40.08	49.98	57.88	66.36
5	Subtherapeutic	63.20	51.24	38.62	28.22	21.14	14.92	9.98
	Therapeutic	20.36	23.26	27.32	25.96	24.58	21.36	18.26
	Toxic	16.44	25.50	34.06	45.82	54.28	63.72	71.76

[a]Grade of renal function classified as follows: 1, eGFR $\geq$90; 2, 60$\leq$eGFR$\leq$89; 3, 30$\leq$eGFR$\leq$59; 4, 15$\leq$eGFR$\leq$29; 5, eGFR<15.

[b]Target attainment classified as follows: subtherapeutic: C_{peak}<35 ug/mL and $C_{trough}\leq$4 ug/mL; therapeutic: 35 ug/mL$\leq C_{peak}\leq$45 ug/mL and $C_{trough}\leq$4 ug/mL; toxic: C_{peak}>45 ug/mL or C_{trough}>4 ug/mL

Table 5. Probabilities of target attainment from model-based simulation of amikacin pharmacokinetic profiles followed 5 times administration of amikacin by various intermittent dosing regimen.

Grade[a]	Target attainment[b]	17 mg/kg	18 mg/kg	19 mg/kg	20 mg/kg	21 mg/kg	22 mg/kg	23 mg/kg	24 mg/kg	25 mg/kg
1	Subtherapeutic	67.54	60.54	55.42	48.88	43.26	37.94	32.42	27.72	24.40
	Therapeutic	18.00	19.74	21.66	23.34	24.00	24.98	23.28	23.10	21.94
	Toxic	14.46	19.72	22.92	27.78	32.74	37.08	44.30	49.18	53.66
2	Subtherapeutic	66.26	59.56	53.60	47.00	42.54	36.64	32.48	26.10	23.38
	Therapeutic	19.22	20.56	22.48	24.04	23.26	24.18	23.06	23.56	22.06
	Toxic	14.52	19.88	23.92	28.96	34.20	39.18	44.46	50.34	54.56
3	Subtherapeutic	64.92	58.88	53.72	47.02	41.22	35.88	32.04	26.86	23.30
	Therapeutic	19.26	20.60	22.98	23.36	23.42	23.04	24.18	23.20	22.04
	Toxic	15.82	20.52	23.30	29.62	35.36	41.08	43.78	49.94	54.66
4	Subtherapeutic	63.54	59.32	53.68	46.22	40.92	35.76	29.10	25.24	22.14
	Therapeutic	18.92	20.68	21.54	22.38	23.50	23.06	23.16	22.22	21.68
	Toxic	17.54	20.00	24.78	31.40	35.58	41.18	47.74	52.54	56.18
5	Subtherapeutic	63.80	57.70	49.94	43.26	38.58	33.60	29.26	24.86	20.94
	Therapeutic	19.02	20.10	22.56	22.86	23.26	23.04	21.88	21.60	20.24
	Toxic	17.18	22.20	27.50	33.88	38.16	43.36	48.86	53.54	58.82

[a]Grade of renal function classified as follows: 1, eGFR $\geq$90; 2, 60$\leq$eGFR$\leq$89; 3, 30$\leq$eGFR$\leq$59; 4, 15$\leq$eGFR$\leq$29; 5, eGFR<15.

[b]Target attainment classified as follows: subtherapeutic: C_{peak}<65 ug/mL and $C_{trough}\leq$4 ug/mL; therapeutic: 65 ug/mL$\leq C_{peak}\leq$80 ug/mL and $C_{trough}\leq$4 ug/mL; toxic: C_{peak}>80 ug/mL or C_{trough}>4 ug/mL.

DISCUSSION

In this study, the optimal pharmacotherapy was explored through analysis of the population PK of amikacin in adult patients diagnosed with NTM-PD. Although amikacin PK has already been studied in populations of various diseases, this is the first study performed in patients with NTM-PD.

In general, a two-compartment pharmacokinetic model was well described concentration-time data for amikacin, but one-compartment model is often used to described amikacin PK with sparse data.[18-21] Although our data were collected through routine therapeutic drug monitoring (TDM) which is sparse data, the 55 blood sample were collected at a time other than sampling time of C_{peak} and C_{trough}. Therefore, the two-compartment model better described our data, with a significant improvement in the OFV and GOF.

In the study, the population CL and V values estimated for amikacin (CL, 3.52 L/h; V, 14.5 L) were similar to those previously described for amikacin in previous study.[19, 20] Therefore, the PK characteristics of amikacin in patients with NTM-PD were similar to those of patients diagnosed with other diseases. Therefore, our model can be applied to other

indications of amikacin.

In this study, eGFR and body weight were important covariates that were shown to influence amikacin CL and V1. As amikacin is excreted mainly through the kidneys, it is reasonable for eGFR to be a covariate for CL.[22, 23] The association between total body weight and the volume of distribution has already been reported, thus it is reasonable to evaluate body weight as a covariate of distribution.[24] As body weight is an influential covariate, it is more suitable to adjust amikacin dose by total body weight.

The dosing regimen should be considered based on a patient's renal function. For the once daily dosing regimen, 12 mg/kg was the most appropriate dosing regimen in patients with normal renal function. However, for patients with the other renal functions, 11 mg/kg was the most suitable dosage, and when 12 mg/kg was administered to these patients, the probability of toxicity was approximately 10% greater than for 11 mg/kg. However, when antibiotic treatment is needed considering toxicity based on the patient's condition, a higher dose can be selected based on the judgement of clinicians and guided by on the results of model-based simulation.

In this study, the primary limitation was that the number of patients included in the analysis was not large enough. We searched patients with NTM-PD by primary diagnosis in SUPREME. Therefore, patients with NTM-PD were omitted if their primary diagnosis was not NTM-PD. Although the number of subjects was not large enough, a sufficiently valid model was constructed in this study. The second limitation was that the effect of the concomitant disease and medication on the PK properties of amikacin were not considered in the study. However, no significant interactions of amikacin with other medications have been reported; therefore, the concomitant medication would not be expected to affect the amikacin PK analysis in the general patient population.[8, 10] Also, no changes were made in diagnosis and medications used to treat NTM-PD between 2009 and 2019.[4] Hence, there are no significant differences in the basic treatment of NTM-PD patients.

To the best our knowledge, this is the first study to analyse amikacin PK properties in Korean patients with NTM-PD. The final population PK model provided a good description of the amikacin PK parameters. The proposed amikacin dosing regimen

based on the final model will provide a rationale to individualize optimal dosing and therefore improve the clinical outcomes of amikacin therapy.

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APPENDICES

1. NONMEM control code for the final pharmacokinetic model

```
$SUBROUTINES ADVAN3 TRANS4

$PK
TVCL = THETA(1)*(EGFR/91.1)**THETA(7)
CL =TVCL * EXP(ETA(1))
TVV1 = THETA(2)*(WT/51.1)**THETA(8)
V1 = TVV1 * EXP(ETA(2))
Q = THETA(3)
V2 = THETA(4)
S1 = V1

$ERROR
IPRED = LOG(F+0.0001)
    W = SQRT(THETA(5)**2*IPRED**2 + THETA(6)**2)
    Y = IPRED + W*EPS(1)
 IRES = DV-IPRED
IWRES = IRES/W
```

```
$THETA
(0, 3.52); CL
(0, 14.4); V1
(0, 0.464); Q
(0,14.2); V2
(0.0001) FIX; Prop.RE (sd)
(0, 0.299); Add.RE (sd)
(0, 0.229); EGFR PM
(0.702); WT PM

$OMEGA BLOCK(2)
 0.075; IIV CL
 -0.0135 0.0318; IIV V1

$SIGMA
1 FIX; Proportional error PK

$EST METHOD=1 INTER MAXEVAL=9999 NOABORT SIG=3
PRINT=1 POSTHOC
$COV
```

; Xpose

$TABLE ID TIME TAD TAD1 DV MDV EVID IPRED CWRES IWRES ONEHEADER NOPRINT FILE=sdtab108

$TABLE CL V1 V2 Q ONEHEADER NOPRINT FILE=patab108

$TABLE ID SEX ONEHEADER NOPRINT FILE=catab 108

$TABLE ID AGE HT WT CR ALB EGFR ONEHEADER NOPRINT FILE=cotab 108

국문 초록

서론: 비결핵 항산균은 결핵균을 제외한 항산균을 칭한다. 비결핵 항산균 폐질환은 비결핵 항산균 감염증의 90% 이상을 차지하는 가장 흔한 질환이다. Macrolide 계열의 항생제가 비결핵 항산균 폐질환의 치료에 가장 기본으로 사용되며, macrolide 계열 항생제에 내성을 보이거나 증상이 심하고 광범위한 병변을 가진 환자의 경우 아미카신을 치료제로 사용한다. 아미카신의 집단 약동학 분석은 이미 진행된 바 있으나 비결핵 항산균 폐질환 환자집단에 대한 아미카신 약동학 분석은 시행된 바가 없었으므로 비결핵 항산균 폐질환 환자에서의 아미카신의 집단 약동학 분석을 통하여 비결핵 항산균 폐질환 환자에서의 아미카신의 최적의 치료약물요법을 찾고자 하였다.

방법: 본 연구는 후향적 연구로 치료적 약물 모니터링(Therapeutic Drug Monitoring, TDM)을 진행한 총 70 명의 비결핵 항산균 폐질환 환자의 아미카신의 투여 용법, 혈중 아미카신의 농도, 인구학적정보, 크리아티닌, 신장청소율, 알부민 등 필요한 정보를 서울대학교병원 임상데이터웨어하우스 SUPREME을 활용하여 후향적으로 수집하였다. 비결핵 항산균 폐질환 환자들은 단회 또는 반복으로 아미카신을 정맥투여 하였다. 70명 환자에서 총 848개의 농도 자료가 포함되었으며 해당 데이터는 모두 집단 약동학 분석에

포함되었다. NONMEM을 활용하여 모델 기반 시뮬레이션을 통하여 비결핵 항산균 폐질환 환자에서의 적정약물요법을 탐색하였다.

결과: 2구획 구조모형으로 아미카신의 집단 약동학 특성은 적절히 설명되었다. 사구체여과율(eGFR)과 체중이 공변량으로 평가되었다. 모델기반 시뮬레이션을 진행하였으며 같은 용량용법으로 아미카신 투여하였을 때 체중에 따라 혈청내 아미카신 농도가 낮아지는 경향을 확인할 수 있었다. 본 연구를 통해 제시한 비결핵 항산균 폐질환 환자에서의 용량용법은 eGFR이 정상인 환자들의 경우 12mg/kg 1일 1회 용법이 가장 적절하였으며 eGFR 이 90mL/min/1.73m^2 미만인 환자들의 경우 11mg/kg 1일 1회 용법이 적절한 것으로 판단되었다. 또한 2일 1회 용법의 경우 신장기능이 eGFR 이 60mL/min/1.73m^2 이상인 환자의 경우 22mg/kg으로 투여하는 것이 가장 적절하며 eGFR이 60mL/min/1.73m^2 미만인 환자들의 경우 21mg/kg으로 투여하는 것이 적절할 것으로 사료된다.

결론: 본 연구는 비결핵 항산균 환자에서의 TDM 데이터를 활용하여 비결핵 항산균 환자의 집단 약동학 분석을 진행한 첫번째 연구이다. 최종적으로 개발된 모델을 기반으로 비결핵 항산균 환자의 신기능에 따른 적정약물요법을 제시하였으며 이는 비결핵

항산균 환자의 치료적 성공율을 높일 수 있는 근거로 제시될 수 있다.

주요어: 비결핵 항산균 폐질환, 아미카신, 집단 약동학

학 번: 2017-21491