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A population pharmacokinetic study of intravenous busulfan in pediatric patients undergoing hematopoietic stem cell transplantation

소아 조혈모세포이식 환자에서 정맥투여 부설판의 집단약동학 연구

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A population pharmacokinetic study of intravenous busulfan in pediatric patients undergoing hematopoietic stem cell transplantation

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ABSTRACT

Introduction: The dosage for once-daily intravenous busulfan in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) has been challenging mainly due to the high inter-individual variability of busulfan. This study was conducted to characterize the pharmacokinetics (PK) and identify significant covariates for intravenous (IV) busulfan, and to derive an optimal once-daily IV busulfan dosing nomogram for pediatric patients undergoing HSCT.

Methods: A population PK analysis was performed using 2,183 busulfan concentrations in 137 pediatric patients (age: 0.6 – 22.2 years), who received IV busulfan once-daily for 4 days before undergoing HSCT. Based on the final population PK model, an optimal once-daily IV busulfan dosing nomogram was derived. The percentage of simulated patients achieving the daily target area under the concentration-time curve (AUC) by the new nomogram was compared with that by other busulfan dosing regimens including the FDA regimen, the EMA regimen, and the empirical once-daily regimen without therapeutic drug monitoring (TDM).

Results: A one-compartment open linear PK model incorporating patient's body surface area, age, dosing day, and aspartate aminotransferase as a significant covariate adequately described the concentration–time profiles of busulfan. An optimal dosing nomogram based on the PK model performed significantly better than the other dosing regimens, resulting in >60% of patients achieving the target AUC while the percentage of patients exceeding the toxic AUC level was kept <25% during the entire treatment period.

Conclusions: The once-daily busulfan dosing nomogram suggested in this study performed better than the other regimens in achieving the therapeutic target AUC, which can be useful for clinicians, particularly in a setting where TDM service is not readily available.

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Keywords: Population pharmacokinetic modeling, Intravenous busulfan, Pediatric, Once-daily nomogram

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration–time curve
BSA	body surface area
CI	confidence interval
CL	clearance
CV	coefficient of variation
CWRES	conditional weighted residual
HSCT	hematopoietic stem cell transplantation
IIV	inter–individual variability
IOV	inter–occasion variability
OFV	objective function value
pcVPC	prediction–corrected visual predictive check
PK	pharmacokinetic
RSE	relative standard error
TDM	therapeutic drug monitoring
V	volume of distribution

INTRODUCTION

Busulfan, a bifunctional alkylating agent, has been used as a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (HSCT). Busulfan consists of two labile methane sulfonate groups attached to opposite ends of a four-carbon alkyl chain. In an aqueous solution, busulfan becomes hydrolyzed and releases methanesulfonate groups, which produce reactive carbonium ions that can alkylate DNA.[1] Busulfan causes DNA damage by crosslinking the DNA intrastrand at 5'-GA-3' and 5'-GG-3'. These cross-links can be converted into DNA strand breaks, the process of which is responsible for the cytotoxicity of busulfan.[1,2]

Busulfan has a narrow therapeutic window and its large inter-individual variability can be reduced by intravenous administration.[3,4] The systemic exposure to busulfan is well associated with clinical outcomes.[5] For example, when given four times a day, a busulfan exposure <900 μM·min or 3.69 mg·h/L, as assessed by the area under the concentration-time curve over the dosing interval (AUC_{tau}), increased the likelihood of graft failure and recurrence of disease.[6,7] In contrast, a busulfan AUC_{tau} >1500 μM·min or 6.16 mg·h/L

increased the frequency of hepatic and neurologic toxicities.[8-10] Due to its narrow therapeutic window, however, therapeutic drug monitoring (TDM) is still recommended for busulfan to optimize its dosing regimen. To support this notion, the TDM of busulfan reduced the toxicity of allogeneic HSCT preparative regimens.[11,12]

The utility of busulfan TDM is more obvious in pediatric patients because their pharmacokinetic (PK) inter-individual variability (IIV) is much greater than that in adults.[13] The large inter-individual variability of busulfan PK in children, particularly clearance (CL), can be attributed to a wide range of body size indices in this population (e.g., actual body weight, ideal body weight, and body surface area [BSA]).[13,14] Furthermore, maturation factors such as postmenstrual or postnatal age should be also taken into account. Therefore, previous studies attempted to identify the most significant covariate for the PK parameters of busulfan in the pediatric population in an anticipation of developing a novel dosing nomogram, which might reduce the need for TDM.[15-19] However, it is still controversial which covariate is the most influential in explaining the variability of busulfan PK in children.

Conventionally, intravenous busulfan has been given 4-times daily for four consecutive days. According to the product label of the U.S. Food and Drug Administration (FDA) for busulfan, a 2-step dosing regimen based on body weight based (i.e., 1.1 mg/kg for a body weight of ≤12 kg and 0.8 mg/kg for a body weight of >12 kg) is provided as an initial dose for pediatric patients.[1] Determination of this FDA regimen stems from a population pharmacokinetic study conducted with 24 pediatric patients. Based on the simulation in that study, approximately 60% of patients were expected to achieve the desired target exposure (i.e., AUC_{tau}) of 900 – 1500 μM·min after the initial dosing.[20] On the other hand, the European Medicines Agency (EMA) product label recommends a intravenous busulfan dosing regimen which relies on five body weight categories for pediatric patients (i.e., body weights of <9 kg, 9 to <16 kg, 16 to 23 kg, >23 to 34 kg, and >34 kg).[21] In the population pharmacokinetic study on which the EMA regimen is based, the simulation results predicted that approximately 75% of patients would meet the target AUC_{tau}.[22]

More recently, however, comparable PK and clinical outcomes have been reported between 4-times and once-daily

regimens in both adults and children.[3,4,23] As less frequent administration is certainly more convenient, there have been many attempts to develop a once-daily busulfan dosing regimen.[6,12,24,25,26] In one study, a once-daily busulfan regimen for pediatric patients was prospectively evaluated with respect to clinical outcomes. In that study, the initial BSA-based dose (i.e., 80 mg/m^2 for <1 year of age and 120 mg/m^2 for ≥1 year of age) was given as a 3-hour infusion, and then TDM was conducted to optimize the following three doses. As a result, higher survival and event-free survival rates were obtained by the empirical once-daily dosing with dose adjustment to a total AUC of approximately 79.61 mg·h/L for four days.[12] In another study, using this empirical once-daily regimen with TDM, favorable outcomes were obtained in 44 pediatric patients who underwent HSCT. In detail, the one-year overall survival and event-free survival rates of all patients exceeded 80%, with a median total AUC of approximately 74.82 mg·h/L for four days.[26] Despite these previous reports, a once-daily regimen of intravenous busulfan has rarely been used, particularly in children, due to the lack of consensus as to which covariate the dosing nomogram should be based on.

Based on this understanding, the objectives of the present study were 1) to characterize the PK of once-daily intravenous busulfan, 2) to identify significant covariates that might affect the PK parameters of busulfan, and 3) to derive an optimal once-daily dosing nomogram for intravenous busulfan in pediatric patients undergoing HSCT. To this end, a population PK analysis was performed, coupled with simulation experiments for various busulfan dosing regimens in that population.

METHODS

Patients and treatments

Concentration data of busulfan were retrospectively collected from pediatric patients who underwent HSCT and TDM at Seoul National University Children's Hospital, Seoul, Korea. This study was approved by the Institutional Review Board of Seoul National University Hospital (H- 1310-121-532).

Busulfan was administered intravenously over 3 hours once daily for 4 consecutive days, and PK blood samples were obtained at 0, 1, 2, and 4 hours after the end of infusion. The dose of busulfan on day 1 was calculated based on patient's age and BSA (i.e., 80 mg/m^2 for <1 year, and 120 mg/m^2 for ≥1 year), while the busulfan doses on days 2-3 were derived as the product of the daily target AUC (i.e., 18.75 mg·h/L [4568 μM·min]) and CL on the previous day estimated using a 1-compartment open linear PK model implemented in Phoenix WinNonlin (version 6.3, Certara, St Louis, MO, USA). The busulfan dose on day 4 was the total target AUC (i.e., 75.00 mg·h/L [18270 μM·min]) less the cumulative AUC over the previous 3 days, multiplied by the estimated CL on day 3.[12,25]

The target AUCs were set as proposed in the literature, which showed favorable outcomes in pediatric and infant patients.[26]

Population PK analysis

A population PK model was developed using NONMEM (version 7.2, ICON Development Solutions, Ellicott City, MD, USA) and the First-Order Conditional Estimation with Interaction was the estimation method. Because there were only 4 sampling points after busulfan administration, a one-compartment open linear PK model with first-order elimination was developed.

The observations were expressed as follow:

$$OBS_{ij} = f(P_i, D_i, t_{ij}) \times (1 + \epsilon_1) + \epsilon_2 \quad \text{(Eq. 1)}$$

, where OBS_{ij} is the jth observation (busulfan plasma concentration) in the ith individual; f is the unspecified form of the model to be estimated, which is the function of P_i, D_i, and t_{ij} ; P_i is the set of PK parameters for the ith individual; D_i is the administered dose for the ith individual; t_{ij} is the time of collection, after administration, of the jth observation in the ith individual, and the ϵ_1 and ϵ_2 are the residual shift of the observation from the model prediction (random variable

assumed to be symmetrically distributed around 0 with variance σ_1^2 and σ_2^2, respectively).

For each PK parameter, not only IIV, but also inter-occasion variability (IOV), where occasion was defined as a treatment day, was tested in the model as follow:

$$P_{ij} = TVP_j \times exp(\eta_{ij} + \kappa_{ij}) \qquad \text{(Eq. 2)}$$

, where P_{ij} is the jth parameter for the ith individual as predicted by the model; TVP_j is the typical population estimate for the jth parameter; η_{ij} and κ_{ij} are random variables, representing the shift of P_{ij} from TVP_j (inter-individual variability; IIV) and the shift of P_{ij} from one dosing occasion to others (inter-occasion variability; IOV), respectively. These random variables were assumed to be normally distributed with mean 0 and a variance ω^2, an entity to be estimated in the model. For remaining unexplained intra-individual variability, an additive, proportional, and combined additive and proportional residual error models were tested.

The effect of candidate covariates on the PK of busulfan was explored graphically and tested in the model. Age, height, body weight, BSA (i.e., $\sqrt{\text{height (cm)} \times \text{weight (kg)} / 3600}$),[27] total bilirubin, aspartate transaminase (AST), alanine

transaminase (ALT), serum creatinine, and ferritin were continuous candidate covariates, and sex and dosing day were categorical candidate covariates. Covariate model building was performed in a stepwise fashion with forward selection followed by backward elimination.

Continuous variables (i.e., height, body weight, BSA, bilirubin, AST, ALT, creatinine, and ferritin) were added into the model using the power functions (Eq. 3) except for age, which was included in the model using an exponential asymptotic model (Eq. 4):

$$TVP_j = \theta_n \times \left(\frac{Var_j}{Median\ or\ typical\ value}\right)^{\theta_m} \quad \text{(Eq. 3)}$$

$$TVP_j = \theta_n \times \left(1 - \exp\left(-\frac{\ln(2)}{\theta_m} \times Age_j\right)\right) \quad \text{(Eq. 4)}$$

, where θ_n represents the baseline population parameter estimate not explained by any of the included covariates, Var_j represents the continuous variable in the jth patient that is normalized by the median or a generally accepted typical value (e.g., 70 kg for body weight) of the covariate, and θ_m represent the exponents of the power functions, while θ_m in Eq. 4 represent the maturation half-life of the age-related changes of the PK parameter.

Categorical variables (i.e., sex and dosing day) were added to the model using the following equation:

$$TVP_j = \theta_n \times (1 - \theta_m \times Var_j) \qquad \text{(Eq. 5)}$$

, where θ_n represents the baseline population parameter estimate under reference covariate condition (i.e., Var_j is 0), Var_j represents the discrete variable value in the jth patient, and θ_m represents the scaling factor for the covariate effects. For sex, Var_j is 1 if female, otherwise 0. For dosing day, θ_m was estimated independently in each dosing day, except for day 1 for which Var_j is 0.

Each covariate was added to the base model one at a time during forward selection. A decrease in the objective function value (OFV) of at least 3.84 (χ^2, $P \leq 0.05$ with 1 degree of freedom) was considered significant for adding a single covariate into the model. The full model was developed by incorporating all significant covariates, and each covariate from the full model was deleted one at a time to obtain the final model using the backward elimination procedure. An increase of OFV from the full model of at least 6.63 (χ^2, $P \leq 0.01$ with 1 degree of freedom) was used as the criterion to retain the covariate in the model.

Model qualification

The medians of the PK parameters repeatedly fit using 1,000 resampled bootstrap data sets were compared with the parameter estimates of the final PK model to evaluate its stability. Furthermore, the 95% confidence intervals (CIs) were constructed as the 2.5th and 97.5th percentiles of the bootstrapped estimates. Finally, prediction-corrected visual predictive checks (pcVPCs) were performed, and the observed 5th, 50th, and 95th percentiles were plotted against their respective simulated 95% CIs. The bootstrap procedures and pcVPCs were performed using Perl-speaks-NONMEM (PsN, version 3.6.2).[28]

Performance comparison of busulfan dosing regimens

Using the final population PK model, the PK profiles of various busulfan dosing regimens were simulated using Trial Simulator (version 2.2.2, Certara, St Louis, MO, USA), where parameter uncertainty was also taken into account (Appendix 1). The percentage of simulated patients whose AUC values fell within

±20% of the daily and total target AUCs (i.e., 15 – 22.5 mg·h/L [3654 – 5481 μM·min] and 60 – 90 mg·h/L [14616 – 21924 μM·min], respectively) was compared between the following four dosing regimens for busulfan (Table 1): 1) the FDA regimen[1]; 2) the EMA regimen[21]; 3) the empirical once-daily regimen without TDM, for which patients were assumed to receive the same once-daily dose for 4 days; and 4) an optimal BSA maturation nomogram.

To devise the optimal once-daily dosing nomogram, the empirical Bayes estimates of daily CL were obtained using the final population PK model in virtual patients. In the nomogram, age was categorized into 9 groups (i.e., <1, 1 – 1.33, 1.33 – 1.67, 1.67 – 2, 2 – 3, 3 – 5, 5 – 7, 7 – 11, and ≥11 years), in each of which the estimates of daily CL were similar. Then, a once-daily intravenous busulfan dose was the product of the BSA-normalized daily CL and the daily target AUC of 18.75 mg·h/L.

Table 1. Summary of busulfan dosing regimens

Dosing regimen	Description
FDA regimen	2 h infusion at 1.1 mg/kg for a body weight of ≤12 kg and 0.8 mg/kg for a body weight of >12 kg, repeat every 6 h for 4 days
EMA regimen	2 h infusion at 1 mg/kg for a body weight of <9 kg, 1.2 mg/kg for a body weight of 9 to <16 kg, 1.1 mg/kg for a body weight of 16 to 23 kg, 0.95 mg/kg for a body weight of >23 to 34 kg, and 0.8 mg/kg for a body weight of >34 kg, repeat every 6 h for 4 days
Empirical once-daily regimen without TDM[a]	3 h infusion at 80 mg/m^2 for <1 year of age and 120 mg/m^2 for ≥1 year of age, repeat once daily for 4 days
Optimal BSA maturation nomogram	3 h infusion at a BSA-based dose by age in Table 4, repeat once daily for 4 days

[a] Patients were assumed to receive the same once daily-dose for 4 days.

TDM: therapeutic drug monitoring

BSA: body surface area

RESULTS

Patient demographics

A total of 2,183 samples obtained from 137 patients (70 males and 67 females) 0.6 to 22.2 years of age were available for PK evaluation (Table 2). The majority of patients (96.4%) were younger than 18 years. The mean (range) of body weight, height, and body surface area were 32.8 kg (7.4 – 76.2 kg), 126.9 cm (65.2 – 181.9 cm), and 1.06 m^2 (0.37 – 1.92 m^2), respectively. The most frequent diagnosis was acute leukemia (70.8%).

Table 2. Baseline demographic and clinical characteristics of study patients

Variables	Mean ± SD	Range	Number of patients (%)
Sex			
Male			70 (51.1)
Female			67 (48.9)
Age (years)	8.9 ± 5.4	0.6 – 22.2	
Body weight (kg)	32.8 ± 19.2	7.4 – 76.2	
Height (cm)	126.9 ± 32.0	65.2 – 181.9	
BSA (m^2)	1.06 ± 0.44	0.37 – 1.92	
Total bilirubin (mg/dL)	0.43 ± 0.29	0.10 – 2.50	
AST (U/L)	26.4 ± 13.3	9.0 – 93.0	
ALT (U/L)	26.9 ± 19.8	3.0 – 92.0	
Serum creatinine (mg/dL)	0.44 ± 0.43	0.10 – 5.10	
Ferritin (μg/L)	902.8 ± 1589.3	2.7 – 16778.8	
Diagnosis			
Acute leukemia			97 (70.8)
Other malignancy			17 (12.4)
Congenital disease			15 (10.9)
Myelodysplastic syndrome			4 (2.9)
Others			4 (2.9)

BSA: body surface area

AST: aspartate transaminase

ALT: alanine transaminase

Population PK model

A one-compartment open linear model with proportional residual variability adequately described the observed concentration-time profiles of intravenous busulfan in subjects (Appendix 2). IIVs for CL and volume of distribution (V) were included in the final PK model, while IOV was included only for CL. A covariance term between the IIVs of CL and V was also estimated in the final PK model (Table 3, Appendix 3).

BSA, modeled using a power term, was a significant covariate for CL and V. In addition, age, AST and dosing day also improved the fit significantly when they were included as a covariate for CL. For example, the effect of maturation on the CL of busulfan was incorporated into the final PK model such that the typical adult CL value would be achieved approximately at 2.3 years (Figure 1). Furthermore, AST negatively affected busulfan CL; when AST was 93.0 IU/L, the CL of busulfan decreased to 97.1% of that for AST of 40 IU/L. When compared with day 1, the CL of busulfan on days 2, 3, and 4 was decreased by 5.5%, 13.1%, and 8.1%, respectively.

Table 3. Summary of parameter estimates for busulfan in the final population pharmacokinetic model

Parameters	Estimates (RSE)	Bootstrap median (95% CI)
Structural model		
V[a]; Volume of distribution (L)		
θ_1; typical V value with BSA 1.73m^2	43.8 (3.5%)	43.7 (40.8 – 47.3)
θ_5; BSA exponent for V	1.26 (3.4%)	1.26 (1.18 – 1.35)
CL[b] ; Clearance (L/h)		
θ_2; typical CL value for a BSA of 1.73m^2	10.7 (3.8%)	10.6 (9.8 – 11.6)
θ_6; BSA exponent for CL	1.07 (5.2%)	1.06 (0.94 – 1.17)
θ_7; Age reaching 50% of adult CL	0.326 (27.5%)	0.332 (0.048 – 0.568)
θ_8; AST exponent for CL	−0.035 (38.8%)	−0.036 (−0.062 – −0.007)
DAYF ; day effect on CL (cf. DAYF=0 on day 1)		
θ_9; reduction of CL on day 2	0.055 (25.5%)	0.056 (0.031 – 0.079)
θ_{10}; reduction of CL on day 3	0.131 (9.8%)	0.131 (0.108 – 0.154)
θ_{11}; reduction of CL on day 4	0.081 (18.2%)	0.079 (0.051 – 0.109)

Parameters	Estimates (RSE)	Bootstrap median (95% CI)
Inter−individual variability (IIV)		
IIV for V (%CV)	22.6 (6.9%)	22.4 (18.8 − 25.4)
IIV for CL (%CV)	24.0 (6.7%)	23.7 (20.2 − 26.8)
Correlation between IIV on CL and V	0.0405 (15.8%)	0.0396 (0.0272 − 0.0523)
Inter−occasional variability (IOV)		
IOV CL (%CV)	10.4 (6.6%)	10.3 (8.9 − 11.7)
Residual error		
Proportional error (%CV)	7.87 (6.8%)	7.80 (6.88 − 8.88)

[a] $V = \theta_1 \times (BSA/1.73)^{\theta 5}$

[b] $CL = \theta_2 \times (BSA/1.73)^{\theta 6} \times (1-e^{(-0.693/\theta 7) \times AGE}) \times (AST/40)^{\theta 8} \times (1-DAYF)$

RSE: relative standard error

CI: confidence interval as 2.5th and 97.5th percentiles derived from a bootstrap analysis of 1,000 re−sampled datasets

BSA: body surface area

AST: aspartate transaminase

CV: coefficient of variation

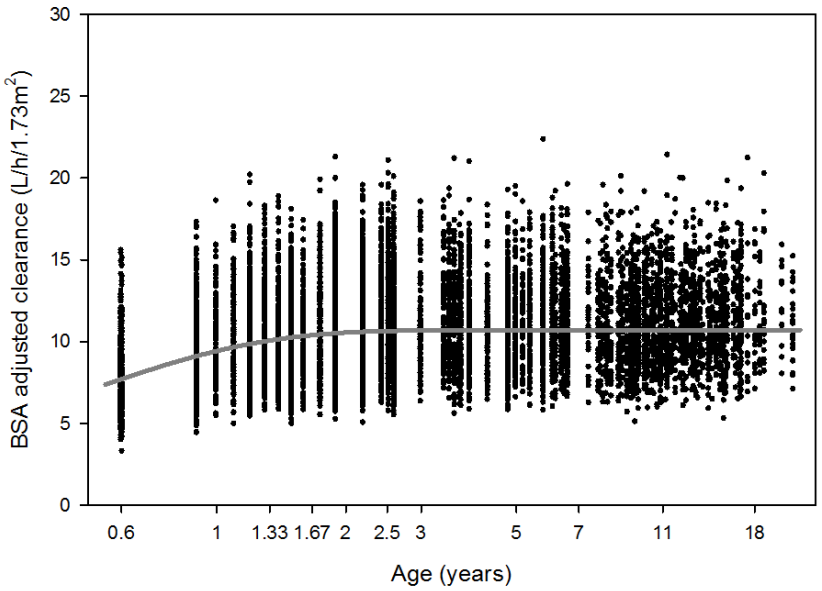

Figure 1. Individual maximum empirical Bayesian estimates of busulfan clearance (adjusted for a typical adult value of 1.73 m^2) versus age. The solid line is the model-predicted maturation function for busulfan clearance.

Model qualification

The population and individual model-predicted busulfan concentrations versus the observed data were spread randomly around the line of identity, indicating that the data were well described by the model (Figure 2). Furthermore, the median parameter estimates obtained from the re-sampled bootstrap datasets were almost the same as the estimates obtained from the final population PK model using the original data set (Table 3). Likewise, the results of the pcVPCs showed that most of the observed concentrations were contained within the 5^{th} and 95^{th} prediction intervals of the simulated concentrations based on the final PK model (Figure 3). Collectively, the final PK model was robust, reliable, and adequate to describe the PK profiles of busulfan after it was intravenously administered once daily for 4 days in pediatric patients undergoing HSCT.

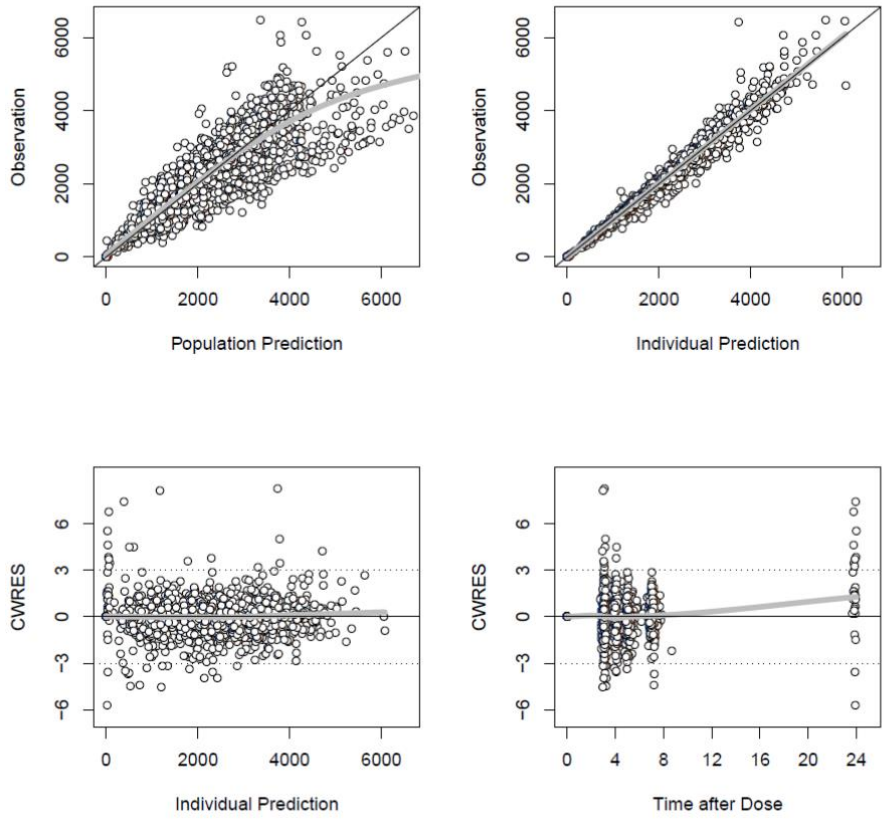

Figure 2. Basic goodness-of-fit plots of the final population pharmacokinetic model for busulfan in pediatric patients undergoing hematopoietic progenitor cell transplantation. Clockwise from the upper left panel are observed values versus population predicted values, observed values versus individual post hoc predicted values, conditional weighted residuals (CWRES) versus time (h) after dose, and CWRES versus individual post hoc predicted values.

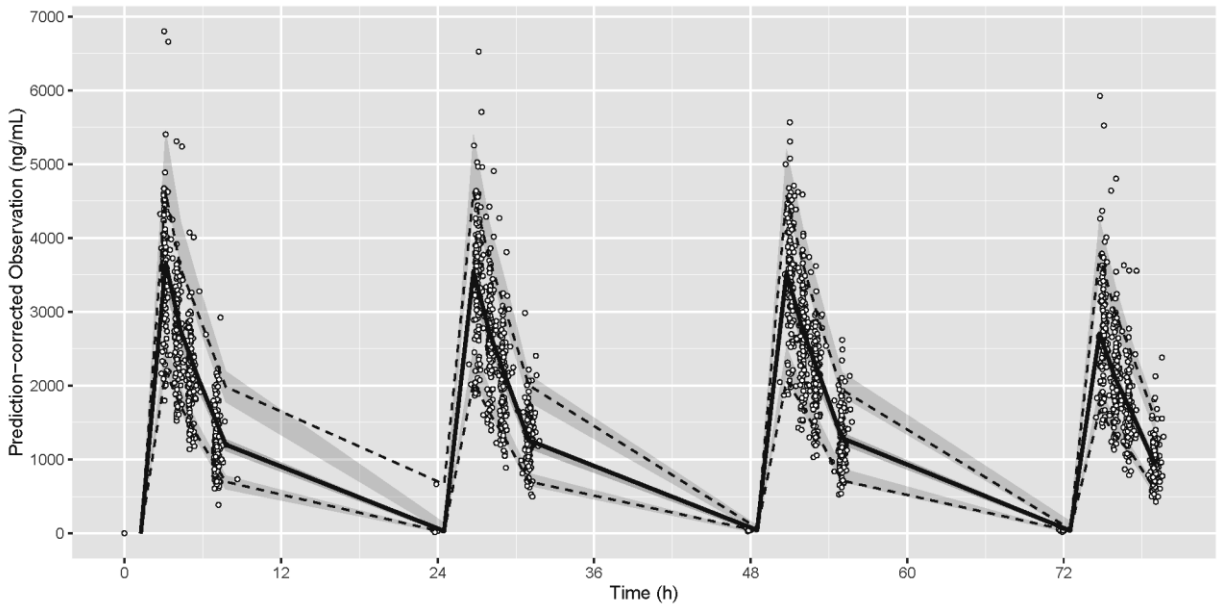

Figure 3. Prediction−corrected visual predictive check for the final model. The empty circles represent the observed concentrations. The dashed and solid lines represent the 5th and 95th percentiles and median of the observed values, respectively, around which the 95% confidence intervals of the simulated values are shown in the shaded area.

Optimal once-daily busulfan dosing nomogram

An optimal dosing nomogram (i.e., BSA maturation nomogram) for busulfan was derived to attain the daily target AUC of 18.75 mg·h/L based on patient's BSA, age, and dosing day (Table 4). The effect of AST was not considered in the optimal dosing nomogram because its effect was relatively small. Compared with the empirical once-daily regimen (i.e., 80 mg/m^2 for <1 year of age and 120 mg/m^2 for ≥1 year of age), the optimal BSA maturation nomogram recommends an 0-19 mg/m^2 lower starting dose on day 1 for age ≥1 year, whereas the recommended dose for age <1 was similar between the two regimens.

Table 4. BSA maturation nomogram for optimal once-daily busulfan dosing

Age (years)	Once-daily busulfan dose per body surface area (mg/m^2)			
	Day 1	Day 2	Day 3	Day 4
< 1	83	79	72	77
1 - 1.33	101	95	87	93
1.33 - 1.67	103	98	90	95
1.67 - 2	108	102	94	99
2 - 3	110	104	95	101
3 - 5	111	105	97	102
5 - 7	113	107	99	104
7 - 11	117	110	101	107
≥ 11	120	113	104	110

BSA: body surface area

Comparison of dosing regimens

Overall, the TDM-supported empirical once-daily regimen, which is the current practice at Seoul National University Hospital, showed the best performance in attaining the target therapeutic AUC range of 15 – 22.5 mg·h/L (3654 – 5481 μM·min) for each day or 60 – 90 mg·h/L (14616 – 21924 μM·min) for 4 days (Figure 4). However, the initial dose of busulfan by this regimen still resulted in only 55% of patients achieving the target AUC range on day 1 while a relatively high percentage of patients (~30%) had an AUC falling in the toxic range (Figure 4-A).

When a fixed daily dose of busulfan was repeatedly administered for 4 days using the FDA regimen, EMA regimen, or the empirical once-daily regimen without TDM, the percentage of patients whose AUC fell within the subtherapeutic, target, or toxic AUC ranges markedly varied day by day (Figure 4-B, C, and D, respectively).

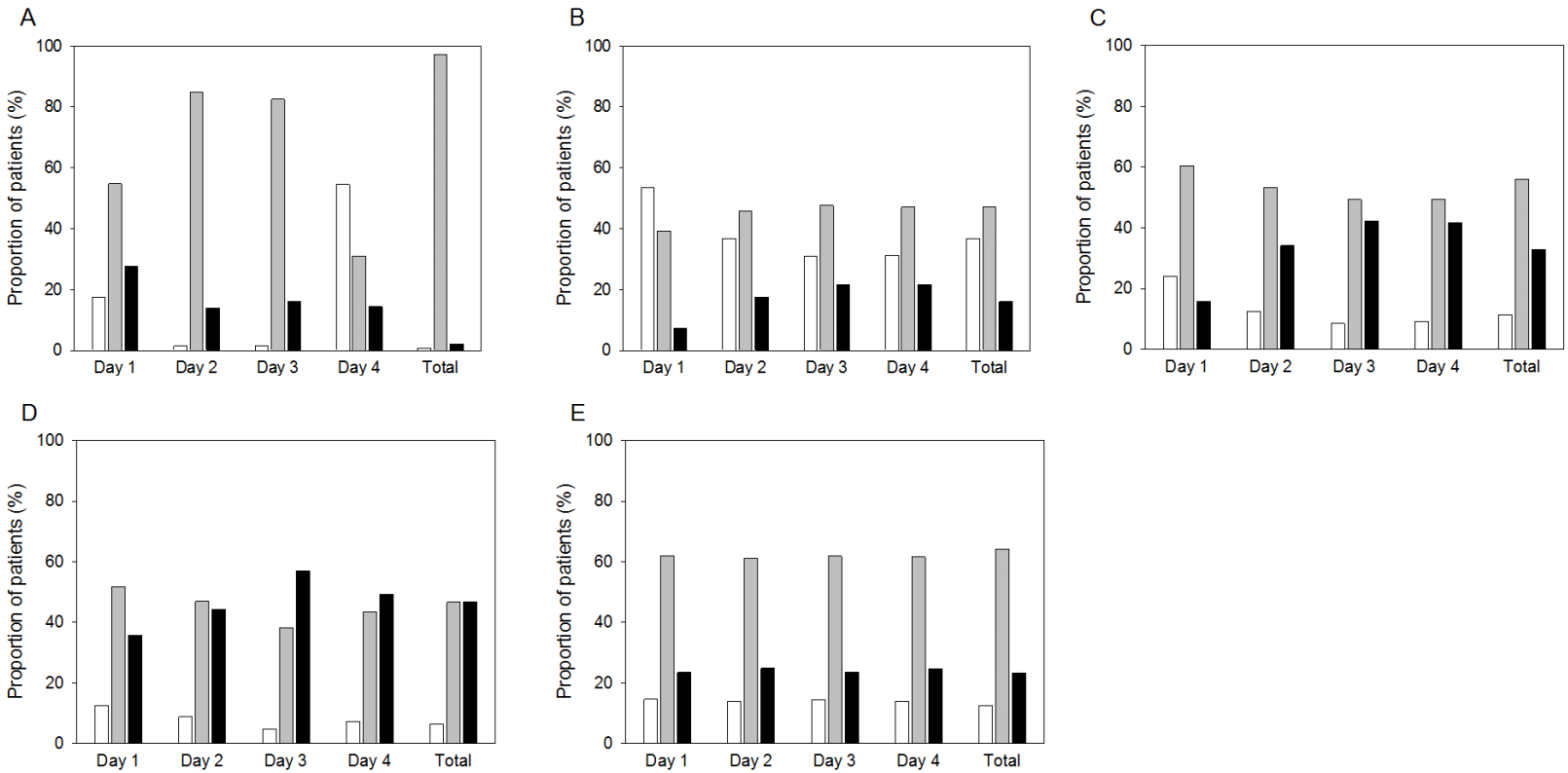
A
B
C
D
E
Proportion of patients (%)
0
20
40
60
80
100
Day 1
Day 2
Day 3
Day 4
Total

Figure 4. Observed (A) and simulated (B–E) percentage of patients achieving the subtherapeutic (white), target (gray), and toxic (black) AUC ranges by day per various busulfan dosing regimens. A (the TDM–supported empirical once–daily regimen); B (the FDA regimen); C (the EMA regimen); D (the empirical once–daily regimen without TDM); and E (the optimal BSA maturation nomogram, see Table 4). The subtherapeutic, target, and toxic AUC ranges were <15 mg·h/L for each day or <60 mg·h/L for 4 days, 15 – 22.5 mg·h/L for each day or 60 – 90 mg·h/L for 4 days, and >22.5 mg·h/L for each day or >90 mg·h/L for 4 days, respectively.

AUC: area under the concentration–time curve

TDM: therapeutic drug monitoring

In contrast, the optimal BSA maturation nomogram (Table 4), which took into account patient's age, body surface area, and daily CL change, steadily resulted in >60% of patients achieving the target AUC while the percentage of patients exceeding the toxic AUC level was kept <25% during the entire treatment period (Figure 4-E). This target AUC-achieving performance of the optimal BSA maturation nomogram was consistently seen in all age groups, whereas the other regimens led to variable and much smaller percentages of patients achieving the target AUC range (Table 5).

Table 5. Percentage of patients achieving the target total AUC for 4 days (i.e., 60 – 90 mg·h/L) by regimen and age

Age (years)	Busulfan dosing regimen			
	FDA regimen	EMA regimen	Empirical once-daily regimen without TDM[a]	Optimal BSA maturation nomogram
< 1	35.2*	37.3*	54.0	60.7
1 – 1.33	62.1	51.1	34.0*	64.7
1.33 – 1.67	63.0	55.1	37.2*	65.2
1.67 – 2	50.6	60.2	44.6	61.9
2 – 2.5	33.2*	58.4	45.5	64.2
2.5 – 3	42.1*	59.8	46.1	64.8
3 – 5	34.8*	60.5	49.9	65.2
5 – 7	40.1*	61.9	48.1	66.5
7 – 11	50.3	57.9	51.9	65.7
≥ 11	60.6	57.7	55.1	63.1
Total	47.2	56.0	46.6	64.2

[a] Patients were assumed to receive the same once daily dose for 4 days

* $P < 0.05$ from χ^2 analysis of the percentage of patients achieving the target total AUC by dosing regimen compared with the optimal nomogram.

AUC: area under the concentration-time curve

TDM: therapeutic drug monitoring

DISCUSSION

In this study, it was found that not only body habitus such as BSA as an anthropometric measure, but also age as a maturation factor should be taken into account when optimizing an intravenous busulfan dose in pediatric patients undergoing HSCT (Table 3, Figure 1). Furthermore, the clearance of busulfan decreases daily up to 13.1% on day 3 after intravenous administration (Table 3). Based on these findings, patient's BSA, age, and dosing day were incorporated into the optimal dosing regimen for busulfan (Table 4), which performed significantly better in achieving the target therapeutic AUC than the other regimens such the FDA regimen, EMA regimen, or the empirical once-daily regimen without TDM (Figure 4, Table 5).

As seen in the present study, substantial daily changes in busulfan CL over the entire dosing period were noted previously.[29,30] This indicates that not only the optimization of the initial busulfan dose, but its daily adjustment is necessary to obtain the best possible therapeutic results in pediatric patients undergoing HSCT. In this sense, TDM-based daily dosing may be still the best option. However, because busulfan is administered over a relatively short period of time (i.e., 4 days),

a rapid dose adjustment based on the calculated CL can be challenging for many clinicians, particularly for those who are working in clinics or hospitals that do not provide prompt TDM service. In this case, the once-daily busulfan dosing nomogram, which incorporated daily CL, such as the one proposed in the present study, can be a useful tool for maximizing the clinical efficacy of busulfan while reducing its toxicity.

Although an optimal initial dose of once-daily busulfan has been proposed several times using the results of population PK studies,[17-19,31] few of them was based on pediatric patients or the number of included children was small. Therefore, the large sample size of pediatric patients included in our population PK analysis could contribute to devising a more reliable and robust dosing regimen for them as demonstrated in terms of achieving the target AUC, particularly the initial dose on day 1 (Figure 4 and Table 5). Based on the optimal BSA maturation nomogram, the busulfan dose on day 1 should be reduced by 3-19 mg/m^2 from the empirical dose for patients 1-11 years of age (i.e., 120 mg/m^2) to lower the percentage of patients whose AUC may fall in the toxic range as shown in Figure 4-A.

The final population PK model adequately described the observed concentration-time profiles for once-daily busulfan dosing in pediatric patients undergoing HSCT. A one-compartment PK model has been reported previously for busulfan PK,[18,31-34] which was preferred to a two-compartment model in the present study as well based on the goodness-of-fit plots. The typical population estimates for CL (10.7 L/h) and V (43.8 L) in this study, standardized for an adult patient weighing 70 kg, were in accordance with those found in the literature.[32-34] Furthermore, the BSA-normalized CL of busulfan matured rather rapidly after birth, reaching the adult value at 2.3 years, which is comparable with the finding of another study that reported the busulfan CL reached 95% of the adult value at 2.5 postnatal years.[19] This agreement in the result strengthens the robustness of the final population PK model, given that the structural model and size scaling factor in the previous study were different from those in the present study.

Because busulfan is mainly metabolized by the glutathione-S-transferase in the liver,[35] liver function could affect the CL of busulfan. To support this notion, AST was

found to be a significant covariate for busulfan CL in this study. A previous study also reported that elevated ALT level reduced the CL of busulfan.[32] Nonetheless, AST was not taken into account in the optimal dosing nomogram in the present study, because the variation of busulfan CL by change in AST was relatively small compared with those caused by other significant covariates such as patient's BSA, age, and dosing day.

Iron overload is frequently seen in patients undergoing HSCT because of repeated blood transfusions, resulting in the increase in serum ferritin. Ferritin is a major intracellular iron storage protein, which hinders iron-catalyzed reactive oxygen species from being generated by chelating excess free iron.[36,37] Therefore, an elevated ferritin level may indicate a prior liver damage owing to iron-generated oxidative stress.[38] A previous study reported that an elevated ferritin level was associated with a high risk of hepatic veno-occlusive disease, which is a major form of busulfan toxicity in those receiving a high-dose busulfan-containing regimen.[36] In addition, an elevated ferritin level is associated with HSCT outcomes (i.e., an increased incidence of non-relapse mortality with decreased overall

survival and relapse-free survival rates).[39] On the other hand, a negative correlation between busulfan CL and ferritin level before HSCT has been suggested in a previous study. In that study, the optimal busulfan dose to meet the target AUC was estimated to be lower for patients with ferritin level ≥1,000 ng/mL than for those with ferritin level <1000 ng/mL.[40] Similarly in this study, an inverse relationship between the ferritin level and busulfan CL was found in the initial covariate search during the forward selection process, though this was eventually removed from the final model because it failed to meet the backward elimination criteria (i.e., P-value ≥0.01). Consequently, although further confirmation is warranted, the possibility of decreased busulfan CL due to an increased ferritin level should be considered in clinical practice, as it may cause busulfan overexposure and possibly affect clinical outcomes.

This study had some limitations. Although children with a wide range of age were included, the number of patients <1 year was small (i.e., n=5, 3.6%) and the minimum age was only 0.6 year. Because busulfan CL is maturated rapidly during 1 year after birth as shown in our model, further studies are warranted to refine the effect of age in neonates, which can

enhance the target AUC-achieving performance of the dosing nomogram for busulfan in that population. Additionally, clinical outcomes such as graft failure and toxicity development should be investigated in a prospective manner to adequately investigate the whole utility of the proposed BSA maturation dosing nomogram.

In conclusion, an optimal dosing nomogram for once-daily intravenous busulfan in pediatric patients undergoing HSCT, which incorporated patient's BSA, age, and dosing day, was successfully developed using a population PK model. The nomogram performed better than the other regimens in achieving the therapeutic target AUC, which can be useful for clinicians, particularly in a setting where TDM service is not readily available or to optimize the initial daily dose on day 1.

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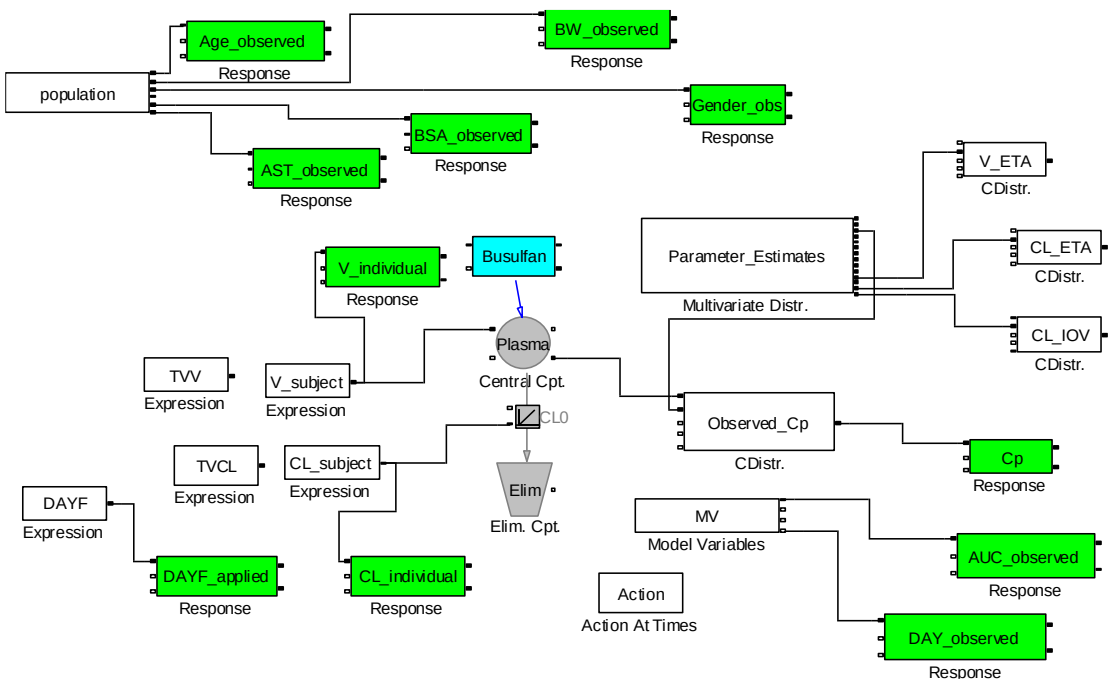
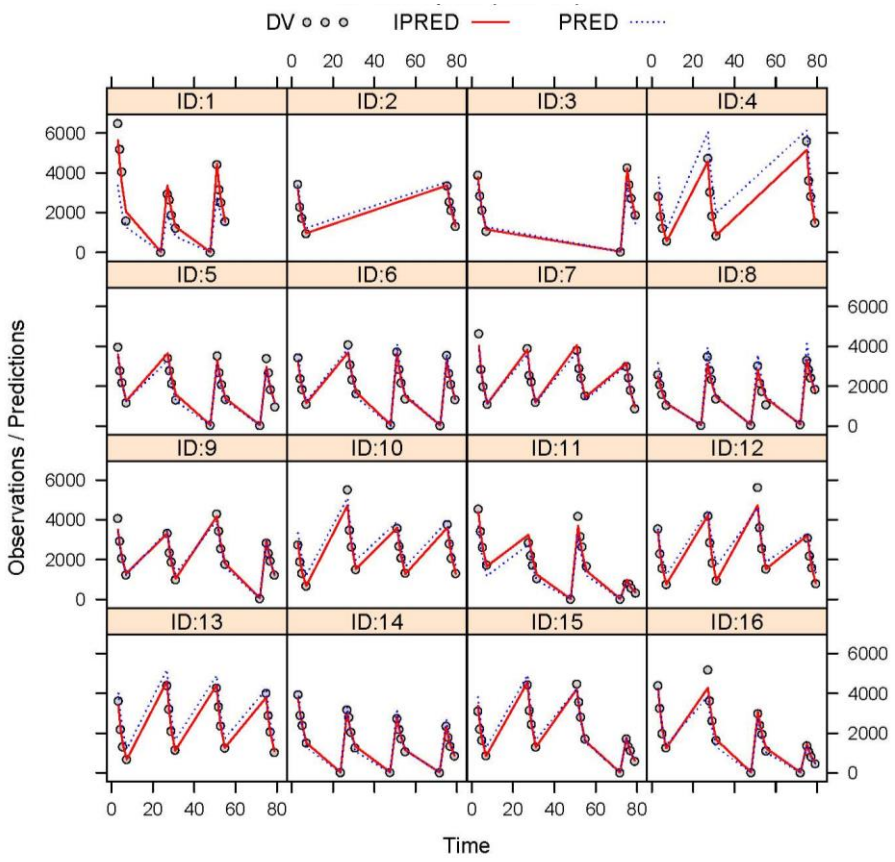
APPENDICES

1. Model structure for simulations



2. Individual fitting plots



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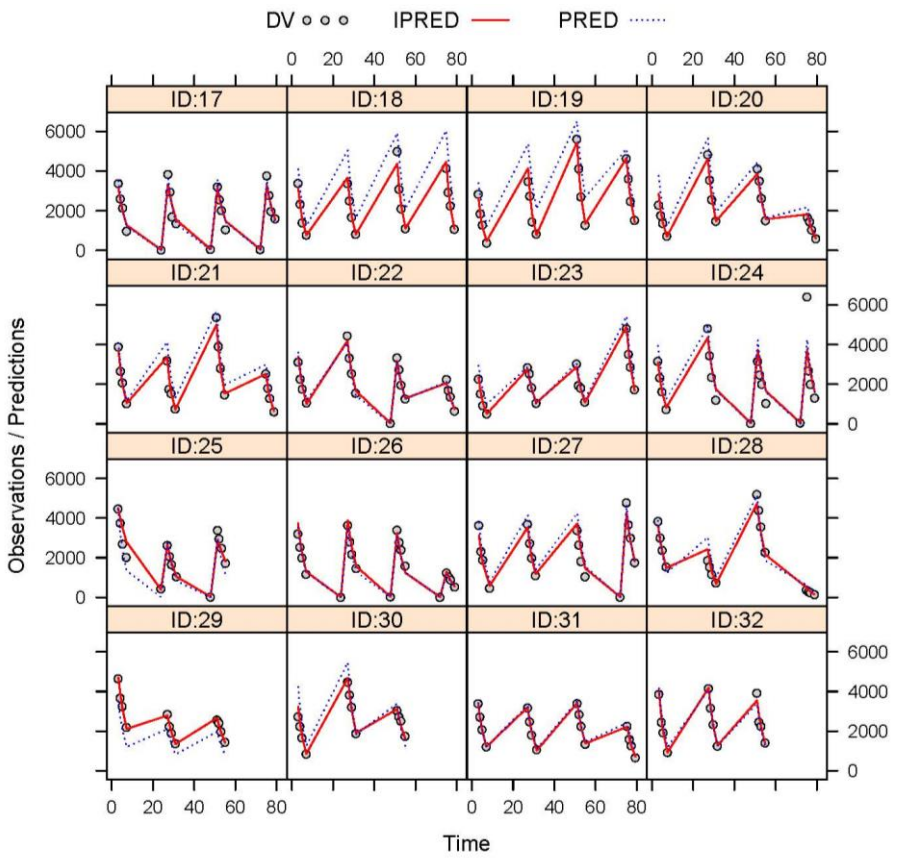

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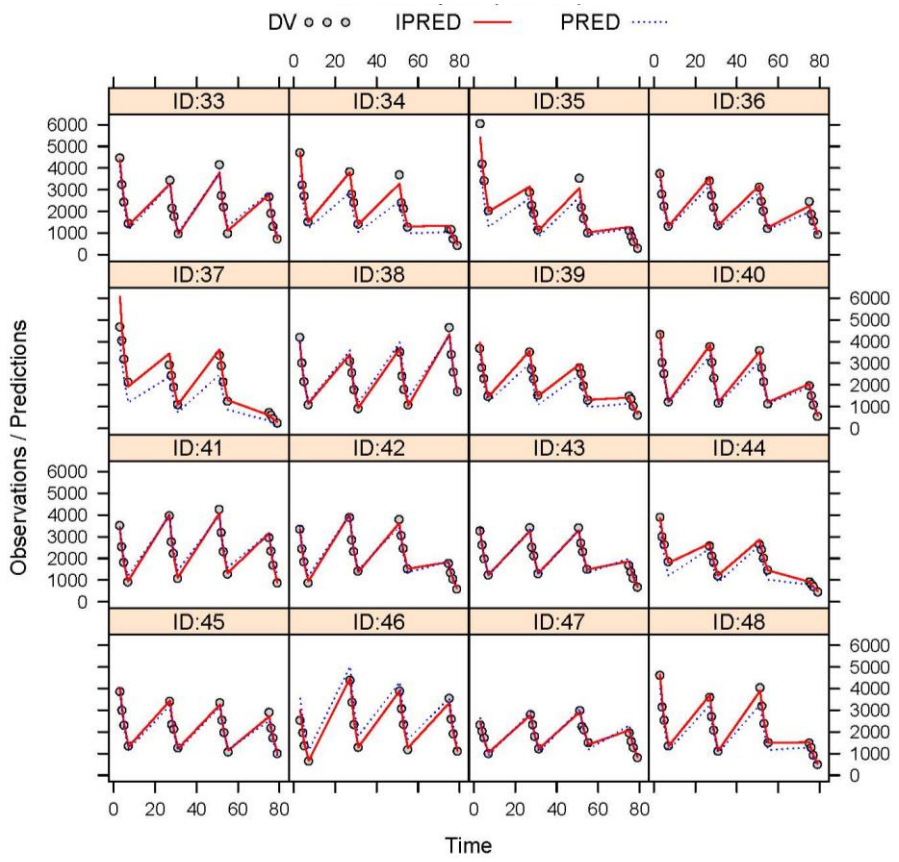

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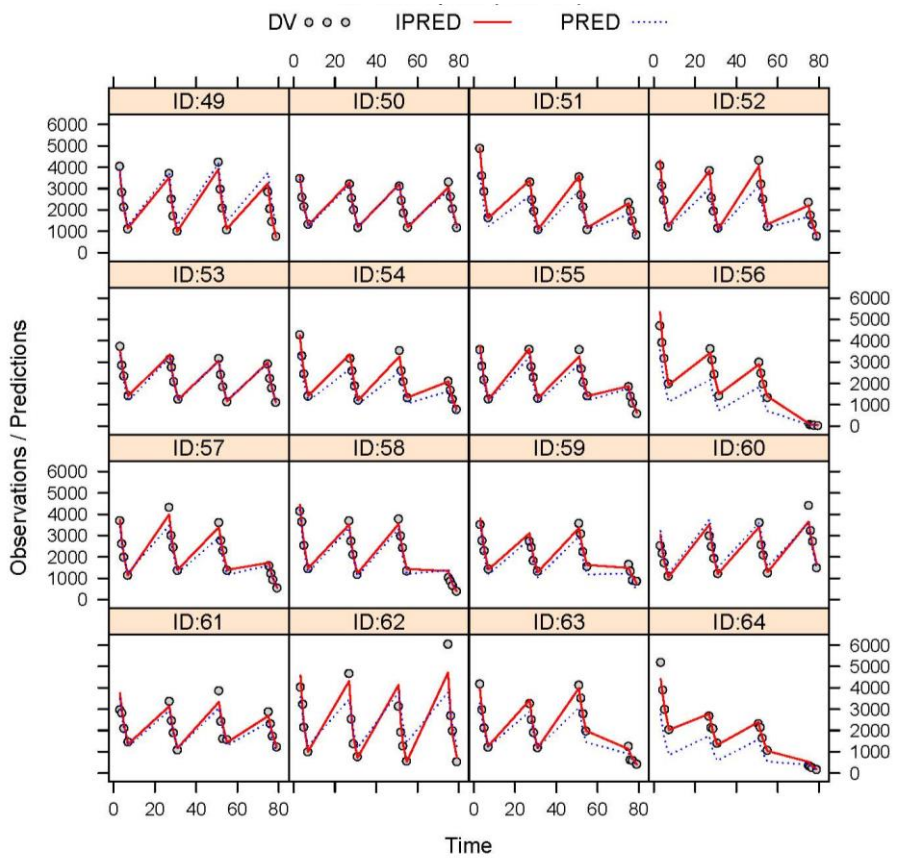

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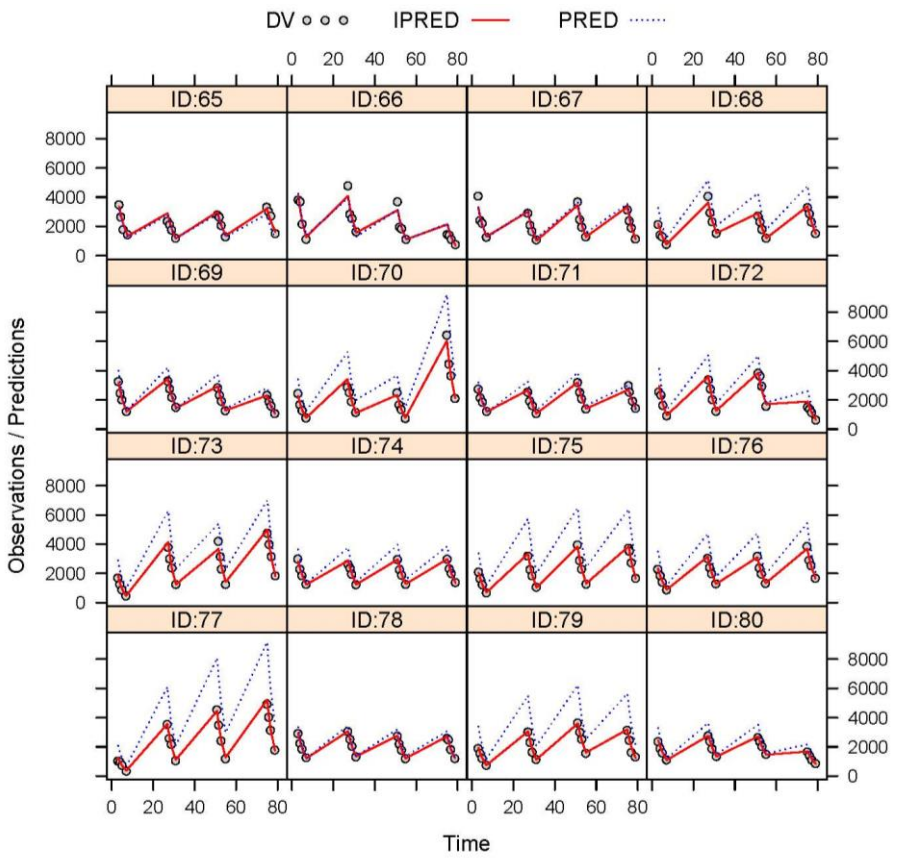

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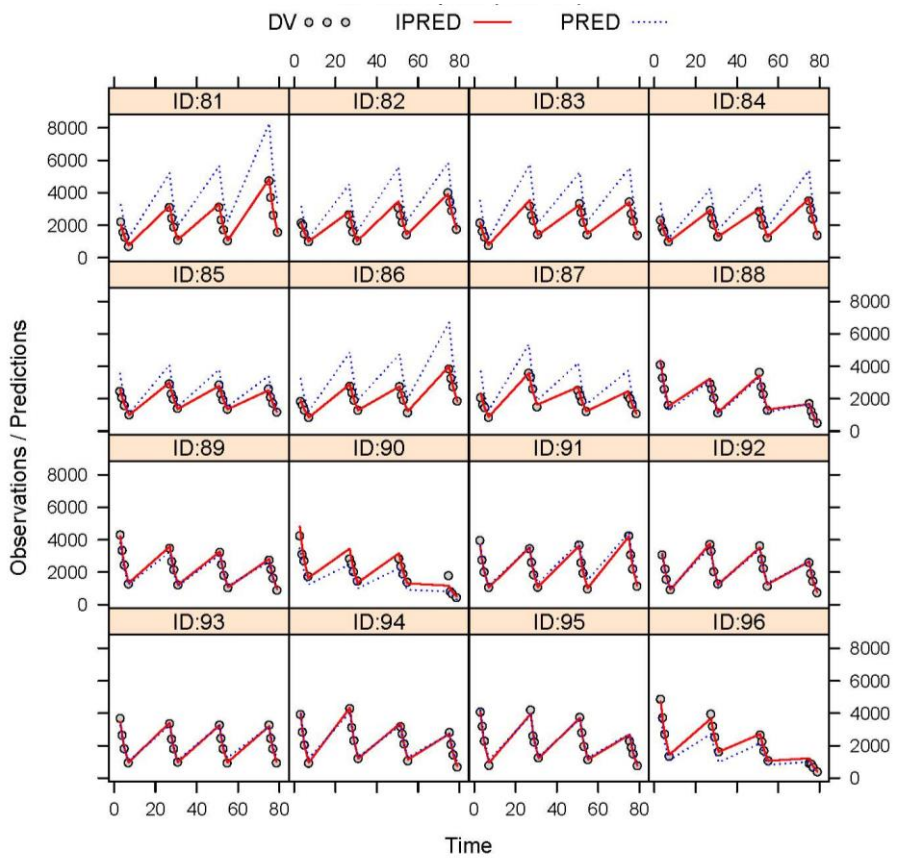

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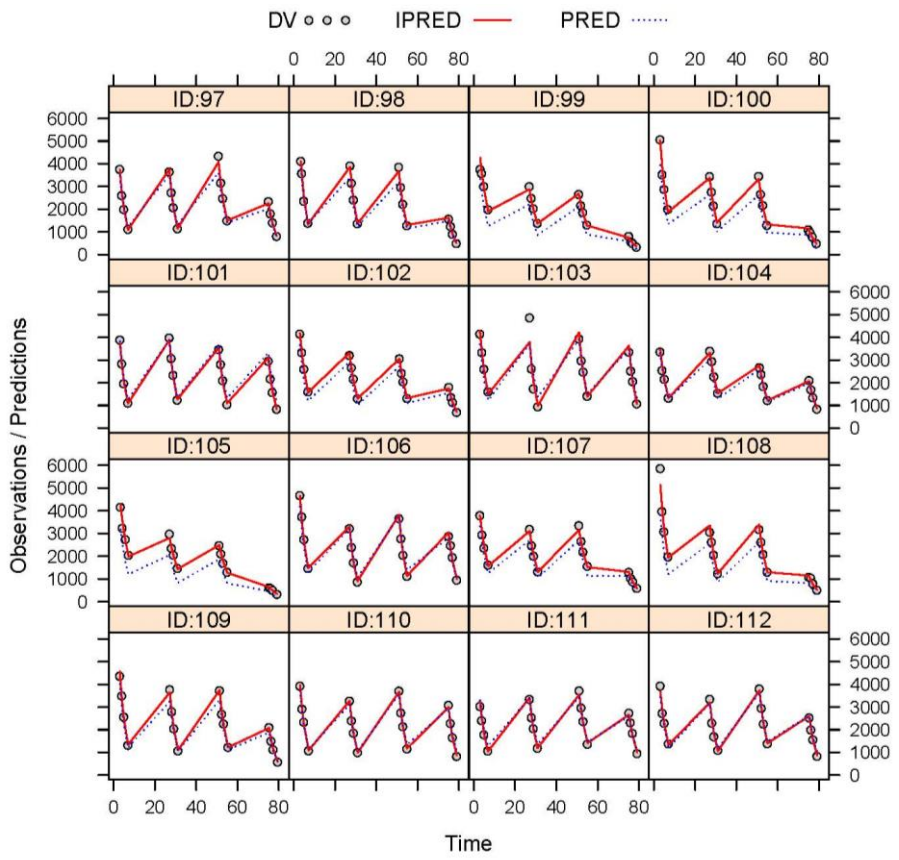

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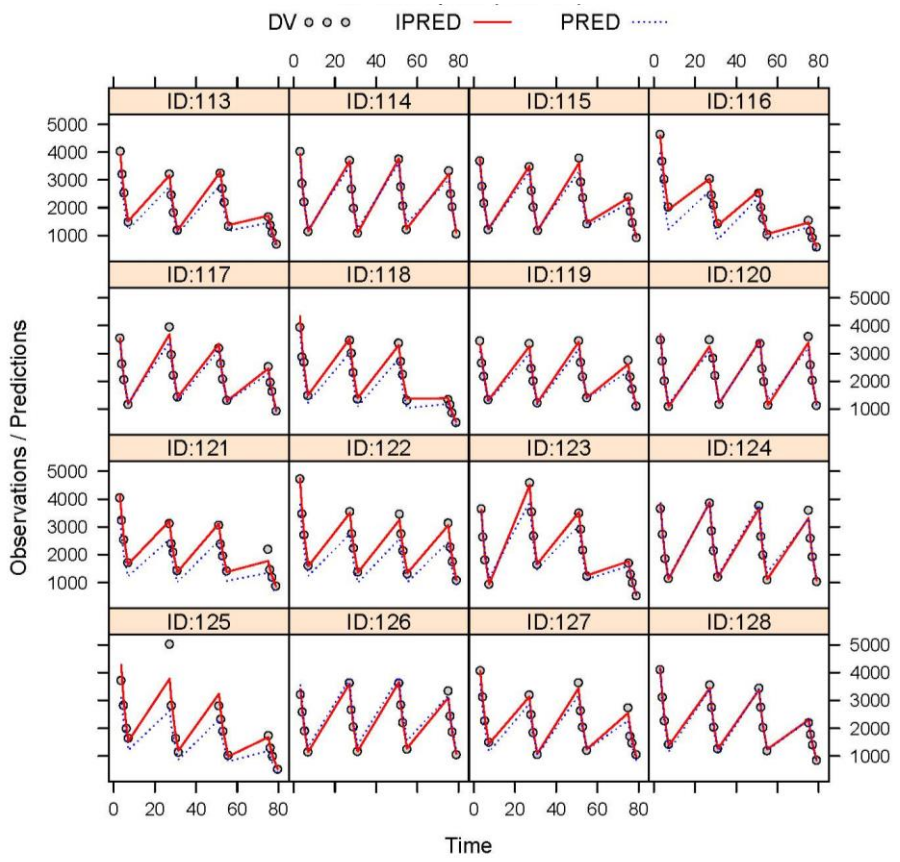

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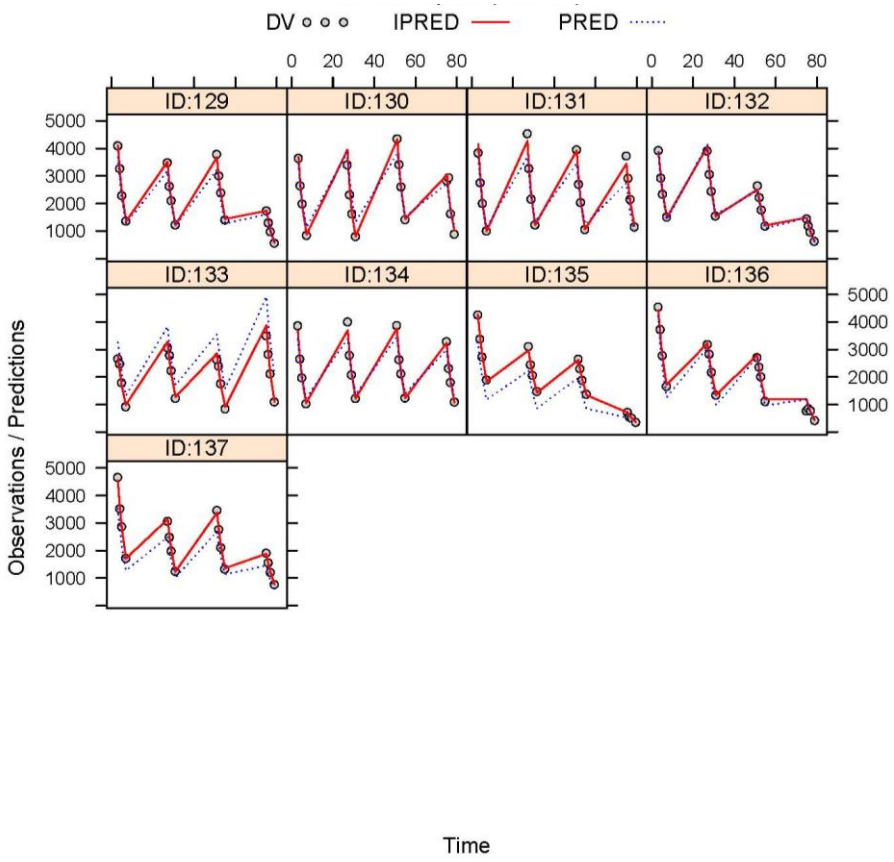

3. NONMEM control for the final model

```
$SUBROUTINES ADVAN1 TRANS2

$PK

;---- FIXED EFFECT DEFINITION ----

TVV = THETA(1) * (BSA/1.73)**THETA(5)

TVCL = THETA(2) * (BSA/1.73)**THETA(6) * (1-EXP(-

(0.693/THETA(7))*AGE)) * (AST/40)**THETA(8) * (1-

DAYF)

IF(DAY.EQ.1)THEN

DAYF=0

ENDIF

IF(DAY.EQ.2)THEN

DAYF=THETA(9)

ENDIF

IF(DAY.EQ.3)THEN

DAYF=THETA(10)

ENDIF

IF(DAY.EQ.4)THEN

DAYF=THETA(11)

ENDIF

;---- RANDOM EFFECT DEFINITION ----

V = TVV *EXP(ETA(1))

CL = TVCL * EXP(ETA(2) + BOVCL)

IF (DAY.EQ.1) THEN

BOVCL = ETA(3)
```

```
ENDIF
IF (DAY.EQ.2) THEN
BOVCL = ETA(4)
ENDIF
IF (DAY.EQ.3) THEN
BOVCL = ETA(5)
ENDIF
IF (DAY.EQ.4) THEN
BOVCL = ETA(6)
ENDIF


SC = V/1000
```

```
$ERROR
IPRED = F
IRES = DV - IPRED
W = SQRT (THETA(3)**2 + THETA(4)**2 * F**2)
IWRES = IRES/W
Y = F + W*EPS(1)
$THETA
(0, 43.8) ; V
(0, 10.7) ; CL
(0.00001) FIX ; ADD
(0, 0.0787) ; PROP
(0, 1.26) ; BSA~V
(0, 1.08) ; BSA~CL
```

(0, 0.309) ; AGE~CL

(−0.0359) ; AST~CL

(0, 0.0554) ; DAY2~CL

(0, 0.131) ; DAY3~CL

(0, 0.0809) ; DAY4~CL

$OMEGA BLOCK(2)

0.0499 ; V

0.0392 0.0531 ; CL

$OMEGA BLOCK(1) 0.0107 ; BOVCL1

$OMEGA BLOCK(1) SAME ; BOVCL2

$OMEGA BLOCK(1) SAME ; BOVCL3

$OMEGA BLOCK(1) SAME ; BOVCL4

$SIGMA

1 FIX

$COVARIANCE

$EST SIG=3 MAX=9999 PRINT=5 METHOD=1 INTER NOABORT

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$TABLE V CL ETA1 ETA2 ONEHEADER NOPRINT FILE=patab001

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국문 초록

서론: 부설판은 조혈모세포이식을 위한 전처치 요법에 사용되는 세포독성 약물로, 치료 약물 농도 범위가 좁으며 개인간 약동학적 변이가 큰 약물로 알려져 있다. 기존에 사용되고 있는 부설판 1 일 4 회 투여 용법에 비해 1 일 1 회 용법을 사용하면, 특히 소아 환자에서 약물 투여의 편리성 등 임상적 유용성을 기대할 수 있다. 이에, 본 연구에서는 소아 환자에 대하여 부설판을 정맥 투여하였을 때 약동학적 특성을 확인하고 유의한 공변량을 탐색하여, 정맥 투여 부설판의 1 일 1 회 용법에 대한 소아 적정 용량을 제안하고자 하였다.

방법: 조혈모세포이식 전 정맥 투여 부설판을 1 일 1 회용법으로 4 일간 투여 받고 약물 농도를 측정한 137 명의 소아 환자 (연령 범위: 0.6 – 22.2 세)에서 총 2,183 개의 약물 농도 자료를 수집하여 집단약동학 분석을 실시하였다. 최종 집단약동학 모델을 바탕으로 정맥투여 부설판의 1 일 1 회 적정 용량을 연령별 및 약물 투여일별로 구분하여 도출하였다. 기존에 소아에 사용되고 있는 정맥투여 부설판의 용법 (FDA 용법, EMA 용법, 경험적 용법)과 집단약동학 모델을 바탕으로 제안된 1 일 1 회 용법을 비교하기 위해, 부설판 투여 시 치료 약물 노출 범위에 도달하는 환자 비율을 시뮬레이션으로 산출하여 비교 평가하였다.

결과: 정맥투여 후 부설판의 시간에 따른 혈중 농도 양상은 일차 속도 소실을 반영한 일구획 모형과 비례 잔차 모형으로 적절하게 설명되었

다. 부설판 분포용적의 개인간 변이에 대한 공변량으로는 체표면적이 유의하였으며, 청소율의 개인간 변이에 대하여는 체표면적, 연령, 약물 투여일, 간기능 검사 수치가 유의한 공변량으로 확인되었다. 최종 집단약동학 모델을 바탕으로 제안된 정맥투여 부설판 1 일 1 회 용법은 다른 기존의 용법들에 비해 치료 약물 노출 범위에 도달하는 환자 비율을 증가시킬 것으로 예상되었다. 즉, 정맥투여 부설판을 각 연령별 적정 용량으로 투여 시, 60% 이상의 환자가 치료 약물 노출 범위에 도달하고, 독성 노출 범위에 해당되는 환자 비율은 25% 미만일 것으로 예상되었다.

결론: 본 연구에서는 집단약동학 분석을 통해 정맥투여 부설판의 약동학적 특성 및 공변량을 소아 환자에서 확인하였으며, 이를 바탕으로 정맥투여 부설판의 1 일 1 회 적정 용량 설정표를 제안하였다. 제안된 부설판 용량 설정표는 치료적 약물 농도 모니터링이 어려운 상황에서 특히 소아 환자의 부설판 적정 투여 용량을 결정하는데 크게 기여할 수 있을 것이다.

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주요어 : 집단약동학 모델링, 정맥투여 부설판, 소아, 1 일 1 회 용법

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