

OBJECTIVES

- Piperacillin-tazobactam is a parenterally administered combination of β -lactam antibiotic/ β -lactamase inhibitor.
- It shows broad antibacterial activity against *Pseudomonas aeruginosa* and other pathogens.
- This combination has been frequently used for the empirical treatment of infection in intensive care patients including burn patients.
- The purpose of this study was to develop a population pharmacokinetic (PK) model for piperacillin in burn patients.

METHODS

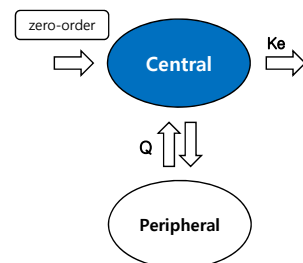
- **Subjects and blood sampling**
 - Patients : Fifty patients with burns ranging from 1% to 81% of total body surface area treated with piperacillin-tazobactam
 - Dosage regimen : 4.5g intravenously infused over 30 min every 8 h
 - Blood sampling : right before and at 1, 2, 3, 4, 6 and 8 h after more than five infusions
- **Population PK modeling**
 - The population PK model was developed using non-linear mixed effect method (NONMEM, ver. 7.2, Icon Development Solutions, USA)
 - First-order condition estimation method (FOCE) with interaction was used throughout the model building
 - Models were selected based upon decrease in the objective function value (OFV) more than 3.84 and improvement in individual plots
 - Final PK model was validated by Bootstrapping and Visual Predictive check (VPC)

Patient Demographics

Characteristics	Mean (range)
No. of patients	50
Age (yrs)	50.14 (20~83)
Sex	M : F = 40 : 10
Weight (kg)	66.9 (50~90)
TBSA (%)	34.56 (1~81)
CRRT (yes/no)	5/45
Edema (yes/no)	16/34
Sepsis (yes/no)	12/38
CL _{CR} * (mL/min)	132.1 (39~231.4)

*CL_{CR} was estimated by Cockcroft-Gault equation.

Final PK Model



Basic Goodness-Of-Fit Plots

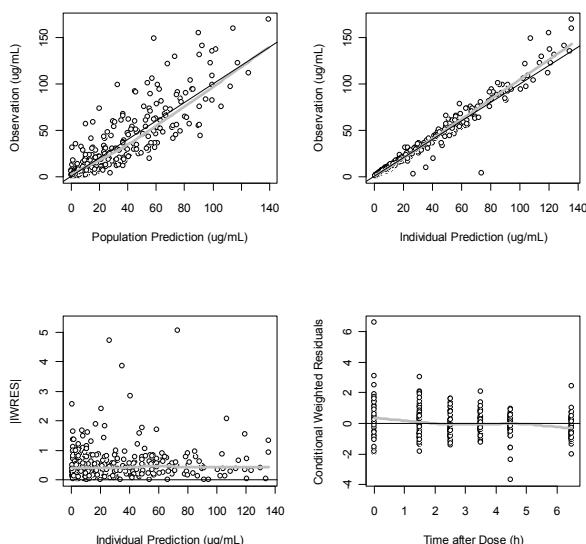


Figure 1. Scatter plots of the final population PK model (circle: observation, black line: line of identity(upper), zero line(lower), gray line: LOESS regression line(all))

Final PK Parameter Estimates

Parameter	Estimate	% RSE	Bootstrap median (95% CI)
Structural model			
TVCL = $\theta_1 \cdot (\text{CLCR}/132)$			
θ_1	15.0 L/h	5.61	14.9 (13.1 – 16.6)
TVV1 = $\theta_2 - \text{SEPSIS} \times \theta_7$			
θ_2	24.6 L	8.09	24.4 (20.3 – 29.6)
θ_7	16.3 L	31.47	15.1 (5.6 – 27.2)
V2	14.6 L	27.05	11.9 (4.5 – 377.4)
Q	0.645	20.78	0.7 (0.4 – 1.8)
Interindividual variability			
ω_{CL}	36.0 %	19.34	35.2 (28.6 – 43.2)
ω_{V1}	38.3 %	38.61	34.6 (17.6 – 54.4)
ω_Q	93.7 %	40.0	96.8 (10.5 – 203.2)
Residual error			
σ_{add}	0.357 ug/mL	42.30	0.0 (-0.5 – 0.5)
σ_{prop}	18.8 %	19.26	18.1 (-11.7 – 24.8)

*95% CI estimated by applying the final population PK model to 1000 re-sampled datasets

Visual Predictive Check

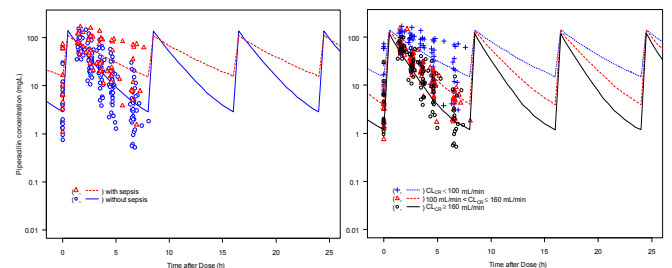
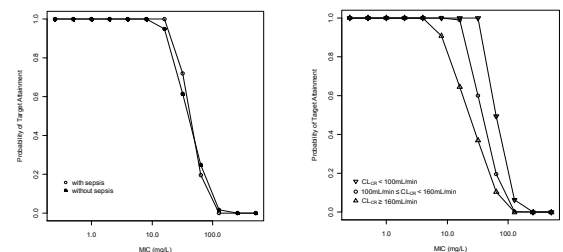


Figure 2. Visual predictive checks of final PK model classified by sepsis (left) and CLCR (right). Symbols, observed data. Lines, median simulated curve.

THERAPEUTIC OUTCOME (Probability of Target Attainment)



CONCLUSION

- The PK of piperacillin have been characterized in burn patients after i.v. infusion.
- The presence of sepsis and the CL_{CR} influenced the predicted probability of target attainment.
- For the optimal piperacillin-tazobactam therapy, patients' current pathophysiologic conditions as well as MIC should be considered.

ACKNOWLEDGEMENT

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REFERENCES

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2. Roberts JA, Kirkpatrick CM, Roberts MS, Dalley AJ, Lipman J: First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. Int J Antimicrob Agents 2010; 35:156-163.