

Population pharmacokinetics of piperacillin in critically ill patients undergoing continuous renal replacement therapies

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OBJECTIVES

The aim of this study was to develop a population pharmacokinetic (PPK) model of piperacillin (PIP) administered to patients of the Intensive Care Unit (ICU) undergoing continuous venovenous hemofiltration.

METHODS

Plasma concentration-time data were obtained from 16 patients who received piperacillin/tazobactam (4 g/0.5 g 20 min-infusion) every 4, 6 or 8 hours. Blood and ultrafiltrate samples were drawn at 0, 0.3, 0.5, 0.75, 1, 3, 4, 6 and 8 hours after dosing and were analyzed using a HPLC-UV validated technique.

The sieving coefficient, defined as the fraction of the drug eliminated across the membrane during continuous renal replacement therapies (CRRT), was calculated as the ratio of area under the ultrafiltrate concentration curve to area under the serum concentration curve. The extracorporeal clearance was estimated as the sieving coefficient times the ultrafiltrate flow.

Piperacillin plasma concentrations were modelled using NONMEM 7 and the FOCE method with INTERACTION. Disposition of the total drug plasma concentration was modelled using compartmental models. Once a base model was selected, patient characteristics including demographic, clinical, and laboratory data were explored for influence on PK parameters. For the model evaluation, parameter precision was evaluated performing a 1000 dataset bootstrap [1]. Visual and numerical predictive check (VPC-NPC) were used to explore model performance of the selected model [2]. One thousand datasets with the same study design as the original dataset were simulated stratified by creatinine clearance.

RESULTS

Sixteen critically ill patients with a mean creatinine clearance (CLcr) of 43 mL/min (range 1.3-110) were enrolled in the study. Piperacillin plasma concentrations (figure 1) were best described by a two-compartment model. The data supported the inclusion of interpatient variability (IPV) in total plasma clearance and the apparent volume of distribution and correlation between them.

Total body clearance included a non-renal, a renal and an extracorporeal component. This extracorporeal component represented about 37% of the total clearance for patients suffering renal failure (CLcr < 10 mL/min), but the relevance decreases at higher values of creatinine clearance (figure 2). Patients body weight resulted a significant covariate for peripheral volume of distribution (Vp). No other covariate was found to improve the model fit. Population parameters and bootstrap results are shown in table 2. Diagnostic plots of the model (npde and CWRES) are shown in figure 3.

The percentage of η - and ϵ -shrinkage was lower than 25 % but a negative value for the total clearance η -shrinkage was shown. This could be due to a small number of patients with rich data [3]. According to the heterogeneity of the ICU patients, high IPV was estimated by the selected model, what performed well with the observations, as shown in the VPC (Figure 4). Results from NPC showed agreement between the 50th simulated percentiles and the medians of raw data for C_{max} and AUC_{0-8} (if CLcr < 20 mL/min, 248.4 mg/L and 1228.9 mg·h/L; and if CLcr ≥ 20 mL/min, 176.2 mg/L and 392.1 mg·h/L, respectively).

Table 2. Population pharmacokinetic parameters of piperacillin after intravenous infusion administration in patients undergoing CRRT.

PARAMETER	Estimate (RSE(%))	Final bootstrap (Mean RSE(%))
$CL (L/h) = \theta_{CL_{nr}} + \left(\frac{CL_{cr}}{2.6}\right)^{\theta_{CL_{cr}}} + CL_{ex}$	$\theta_{CL_{nr}} = 2.68 (31)$ $\theta_{CL_{cr}} = 6.13 (16)$	$\theta_{CL_{nr}} = 2.7 (25)$ $\theta_{CL_{cr}} = 6.05 (18)$
$V_c (L)$	20.8 (21)	20.7 (20)
$Q (L/h)$	20.5 (27)	20.1 (24)
$V_p (L) = (\theta_{Wt})^{W_{GHT}/75.33}$	$\theta_{Wt} = 21.5 (17)$	$\theta_{Wt} = 22.0 (16)$
$IPV_{ca} (\%)$	43 (29)	40.3 (31)
$IPV_{vc} (\%)$	75 (43)	70.1 (40)
Correlation $IPV_{CL} - IPV_{vc} (\%)$	80 (35)	79.8 (37)
Residual error $\sigma_{additive} (log-scale)$	0.193 (11)	0.189 (11)

† Shrinkage (%): $CL_{\eta_{sh}} = -2$; $V_c \eta_{sh} = 3$; $\epsilon_{sh} = 12$

* Included covariates: CLcr (L/h), Weight (kg)

CONCLUSIONS

A two-compartment pharmacokinetic model for piperacillin in patients undergoing continuous renal replacement therapies was developed. Considering that the main objective of antimicrobial treatment is to maintain free-drug plasma concentration above the MIC of the infecting pathogen, this model could be used to determine the probability of PKPD target attainment and to estimate appropriate piperacillin/tazobactam dosage guidelines in these patients.

Acknowledgements

This work was supported by the Departamento de Educación, Universidades e Investigación (IT341-10), Gobierno Vasco, Spain. We would like to thank the Basque Government for research grant awarded to Eduardo Asín.

Table 1. Summary of patient demographic data

Patient characteristic	Mean (SD)	Range
<i>Continuous covariates</i>		
Age (years)	57 (16)	18 - 77
Body weight (kg)	74 (8)	60 - 90
Ultrafiltrate flow (mL/h)	1619 (425)	1000 - 2150
Creatinine clearance (mL/min)	43 (34)	1.3 - 110
Unbound fraction of drug in plasma (%)	78 (13)	48 - 95
Proteinemia (g/dL)	4.7 (0.9)	3.6 - 6.5
Albuminemia (g/dL)	2.15 (0.47)	1.5 - 3.1
Serum bilirubin (mg/L)	2.13 (1.89)	0.4 - 6.7
Sieving coefficient	0.37 (0.25)	0.11 - 1
Extracorporeal clearance (L/h)	0.66 (0.56)	0.13 - 2.1
<i>Categorical covariates</i>		
Sex (%)	Male / Female	75 / 25
SOFA* score		11 (3)
APACHE II** score		22 (6)
Diagnosis of sepsis	Yes / No	11 / 5
Subjects per dosing interval (n)	4h / 6h / 8h	2 / 7 / 5

* SOFA: Sepsis-related Organ Failure Assessment

** APACHE II: Acute Physiology and Chronic Health Evaluation II

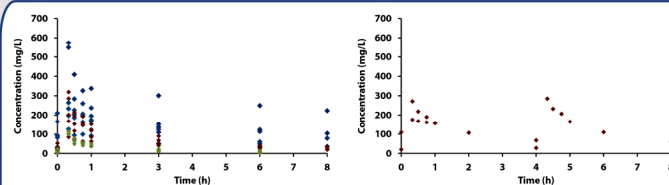


Figure 1. Normal plots of PIP plasma concentration vs. time for the 16 patients. Left panels for 6 - 8 hour dosing interval and right panels for the 2 patients given every 4 h. (Blue: CLcr < 20 mL/min; red: 20 ≤ CLcr < 80 mL/min; green: CLcr ≥ 80 mL/min).

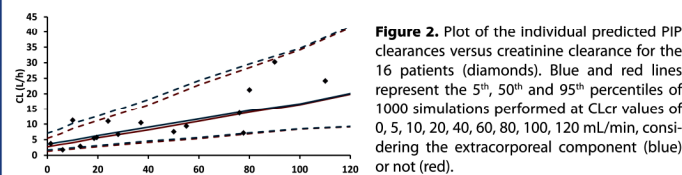


Figure 2. Plot of the individual predicted PIP clearances versus creatinine clearance for the 16 patients (diamonds). Blue and red lines represent the 5th, 50th and 95th percentiles of 1000 simulations performed at CLcr values of 0, 5, 10, 20, 40, 60, 80, 100, 120 mL/min, considering the extracorporeal component (blue) or not (red).

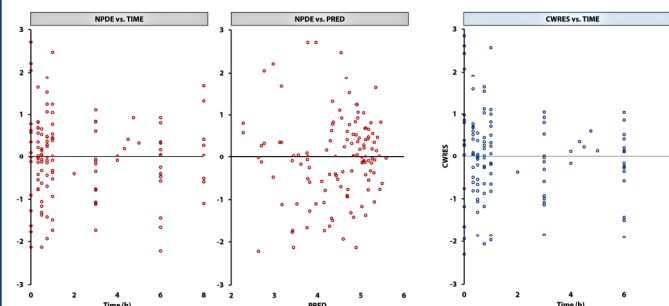


Figure 3. Diagnostic plots: scatterplot of normalized prediction errors (npde) versus time and npde versus population predictions (pred) (left panels). Conditional weighted residuals (CWRES) versus time (right panel).

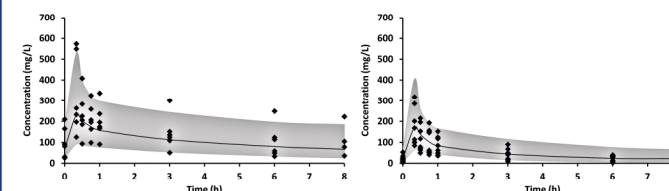


Figure 4. Results from the visual predictive check for patients with CLcr < 20 mL/min (left panel) and with CLcr ≥ 20 mL/min (right panel). Solid line is the median and gray areas cover the 90 % of the simulated profiles for dosing intervals of 6/8h.

References

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