

E. Asín-Prieto, (1,2), A. Sorluce (1,2), A. Rodríguez-Gascón (1,2), H. Barrasa (3), A. Isla (1,2)

(1) Pharmacokinetics, Nanotechnology and Gene Therapy Group, Faculty of Pharmacy, University of the Basque Country (UPV/EHU); Vitoria-Gasteiz, Spain.

(2) Lascaray ikergunea research center, University of the Basque Country; Vitoria-Gasteiz, Spain.

(3) Service of Intensive Care, University Hospital of Alava; Vitoria-Gasteiz, Spain.

OBJECTIVES

The aim of this study was to develop a population pharmacokinetic (PPK) model of daptomycin administered to critically ill patients of the Intensive Care Unit (ICU) for the treatment of infections by *Staphylococcus aureus*.

METHODS

Plasma concentration-time data were obtained from patients who received a dose of 350 or 500 mg of daptomycin every 24 or 48 hours (5.0 to 6.9 mg/kg) administered as a short intravenous infusion. Five blood samples were drawn from each patient at different time points: pre-dose, 0.5 h, 4-8 h, 10-14 h and 24 h. They were analyzed using validated HPLC-UV technique. Demographic and laboratory data were collected including age, gender, body mass index, creatinine clearance, serum albumin or serum bilirubin and are depicted in table 1. The APACHE II score was reported for each patient.

Characteristics	N/N*	Mean ± SD	Median	Range
Demographic data				
Age (years)	-	57±10.79	67	48-83
Gender (Male/Female)	3/7	-	-	-
Weight (Kg)	-	80±16.57	84	54-100
BMI	-	31.17±7.15	30.35	21.1-42.2
Biochemical data				
Creatinine (mg/dL)	-	1.08±0.52	0.9	0.6-1.8
CL _{CR} (mL/min)	-	31±33.81	57.5	20-120
Glucose (mg/dL)	-	200.5±64.43	197	106-299
Hemoglobin (g/dL)	-	8.99±1.16	9.1	7.2-10.9
Hematocrite (%)	-	25.8±3.58	25.4	21-32.9
Albumin (g/dL)	-	2.67±0.42	2.65	2-3.5
PT (s/dL)	-	5.45±0.76	5.25	4.4-6.9
Bilirubin (mg/dL)	-	0.75±0.53	0.6	0.3-0.1
Leucocytes (mm ³)	-	12130±3513	12850	5500-18700
GOT (U/L)	-	40.5±41.93	22.5	15-155
GPT (U/L)	-	43.5±36.83	31.5	6-125
APACHE II	-	-	-	7-30

Table 1. Summary of patient demographic data.

*N/N: ratio of patients; SD: standard deviation; BMI: Body Mass Index; CL_{CR}: Creatinine clearance estimated by the Cockcroft-Gault equation, in case of obese patients, salazar's modified equation was used (1); PT: Total plasma proteins; GOT: glutamic oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; APACHE II: Acute Physiology and Chronic Health Evaluation II, health score associated with the severity of the patients used in the intensive care unit.

Total drug concentrations in plasma were modeled using NONMEM 7.2 and FOCE-I estimation method. Compartmental models were used to fit the data. Once a base model was selected, patient characteristics were explored for influence on PK parameters (table 1). When modelling, the decrease of objective function value (OFV), the relative standard errors of the parameters, the Goodness-Of-Fit plots (GOF) and the performance of simulations support the decision of the selected model. The selected model was evaluated by bootstrap, to study the precision of the estimates (n = 2000, PsN=3.7.6); and the internal validation was tested by visual inspection, performing a prediction and variability corrected visual predictive check (pvcVPC) [2] constructed by representing the observed data versus the simulation (n = 1000) of the final model.

PKPD analysis - Finally, one thousand of studies of 1000 subjects were simulated based on the final model for different degree of renal function (CL_{CR} of 20, 40, 60, 80 and 120 mL/min) in order to estimate the probability of success of the therapy. Doses of 350 mg and 500 mg every 24 h were simulated. Thus, the PKPD index associated with the efficacy of the therapy with daptomycin (AUC/MIC: area under the concentration curve/minimum inhibitory concentration) and the probability of this index was over a value of 666 were estimated for a range of doubling MICs from 0.125 to 8 mg/L [3]. PKPD breakpoints were established when the 5th percentile of the simulations was over the target value [4].

NOTE: Pirana-2.9.0 software was used to assist all the modelling and simulation processes.

RESULTS

Ten patients were analyzed (3 men and 7 women) with an average age of 67 years (from 48 to 83 years) and creatinine clearance (CL_{CR}) from 20 to 120 mL/min. A one-compartment model with first order elimination best fitted the data. Regarding the inclusion of characteristic of the patients in the model, the CL_{CR} resulted in a significant covariate of the daptomycin total plasma clearance (CL), allowing to diminish the unexplained inter-individual variability (IIV) associated to the CL from 51.50% to 31.90%. However, none of the patient characteristics allowed to explain the IIV associated to the volume of distribution (Vd). The population Vd was 8.19 L with an associated IIV of 23.40%. The daptomycin clearance was defined by the next equation: CL (L/h) = 0.267 · CL_{CR}^{0.682}. The proportional error resulted in a 32.7%. Table 2 depicts the population model and the bootstrap results. The GOF plots and the pvcVPC show the model fitting to the observations (figure 1 and 2).

Regarding the PKPD analysis, the probability of target attainment (AUC/MIC > 666) was estimated by simulation based on the final model and it is represented on figure 3. The influence of the creatinine clearance was studied showing differences on the probability of success. In fact, for patients with CL_{CR} of 20 mL/min, it is possible to treat infections by *S. aureus* with MICs up to 1 mg/L. On the other hand, when the renal function is unaltered daptomycin therapy against *S. aureus* with MICs of 0.5 mg/L or higher is unlikely to succeed. The value of the PKPD index is also shown in figure 4 to study the breakpoint for each dose depending on the CL_{CR}.

CONCLUSIONS

A one-compartment pharmacokinetic model best described the data for daptomycin in critically ill patients. The creatinine clearance was a significant covariate of the daptomycin clearance. Based on the simulations, the treatment of patients infected with *S. aureus* with a MIC lower than or equal to 0.25 mg/L with daptomycin will succeed. On the other hand, daptomycin seems not to be an effective therapeutic alternative against *S. aureus* when MICs are higher than or equal to 2 mg/L. Finally, PKPD breakpoints are provided depending on the administered dose and the renal function of the patient.

Table 2. Population pharmacokinetic parameters, including the shrinkage* and the bootstrap results for the daptomycin final model in ICU patients.

PARAMETER	Estimate [RSE(%)]	Bootstrap [Median (5th - 95th percentile)]
CL (L/h) = $\theta_1 \times CL_{CR}^{0.62}$		
θ_1	0.267 (34)	0.260 (0.15 - 0.49)
θ_2	0.682 (31)	0.743 (0.28 - 1.12)
Vd (L)	8.19 (11)	8.08 (6.90 - 9.51)
IIV _{CL} (%)	31.90 (35)	30.49 (7.50 - 47.34)
IIV _{Vd} (%)	23.40 (35)	21.26 (7.57 - 31.46)
RE _{proportional}	0.327 (15)	0.300 (0.23 - 0.38)

CL: apparent total body clearance of the drug from plasma; CL_{CR}: Creatinine clearance; Vd: apparent volume of distribution of the drug; IIV: inter-individual variability; RE: Residual error; RSE: relative standard error; η_{θ_1} = shrinkage value for a parameter; ϵ = shrinkage value for the residual error.

*CL_{CR} = 10%; Vd_{CR} = 26%; ϵ_{θ_1} = 13%

Figure 1. GOF plots corresponding to the daptomycin final model: scatterplot of the observed concentrations versus individual predictions (upper left panel) and population predictions (upper right panel). Conditional weighted residuals (CWRES) versus population predictions (lower left panel) and time after dose in hours (lower right panel).

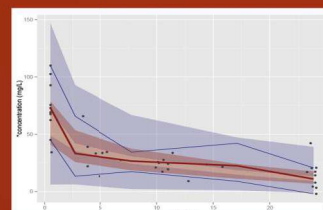
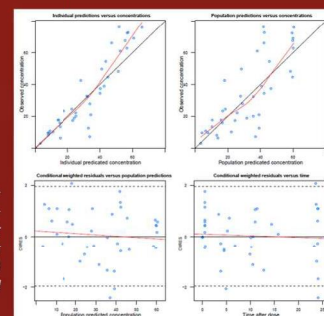


Figure 2. Results of the pvcVPC (n=1000) performed with daptomycin final model. Solid lines represent the 50th percentile (red line) and the 5th-95th percentile (blue lines) of the observations. Red shaded area corresponds to the simulation based 95% confidence interval for the median and the blue shaded areas correspond to the simulation-based 95% percentile for the 5th and 95th percentile. The prediction corrected raw data are represented as black dots. TAD: time after dose.

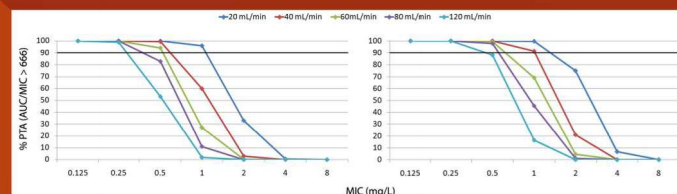


Figure 3. Probability of target attainment (PTA) for daptomycin administered as a short intravenous-infusion (30 min) of 350 mg (left panel) and 500 mg (right panel) every 24 h to patients with creatinine clearances (CL_{CR} of 20, 40, 60, 80 and 120 mL/min). The wider line corresponds to a PTA value of 90% which is related to high success probabilities.

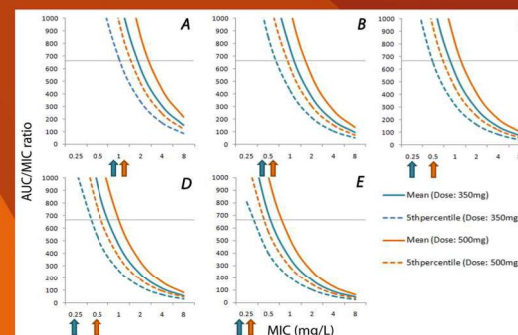


Figure 4. Representation of the PKPD index related with the efficacy of daptomycin (AUC/MIC) versus the value of MIC for simulated patients with different degree of renal function (CL_{CR} of 20 (A), 40 (B), 60 (C), 80 (D) and 120 mL/min (E). The horizontal line represents the value related with bactericidal effect for daptomycin against *S. aureus* (AUC/MIC > 666). Arrows point the PKPD breakpoint for each dose (blue arrow for 350 mg and orange arrow for 500 mg).

References

- [1] Salazar, et al. Am J Med 1988; 84: 1053-1060.
- [2] Karlsson MO, et al. PAGE 17 (2008) Abstr 1434 [www.page-meeting.org/?abstract=1434].
- [3] Safdar N, et al. Antimicrob Agents Chemother 2004; 48 (1): 63-68.
- [4] Mouton JW, et al. Clin Ther 2005; 27: 762-772.

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.